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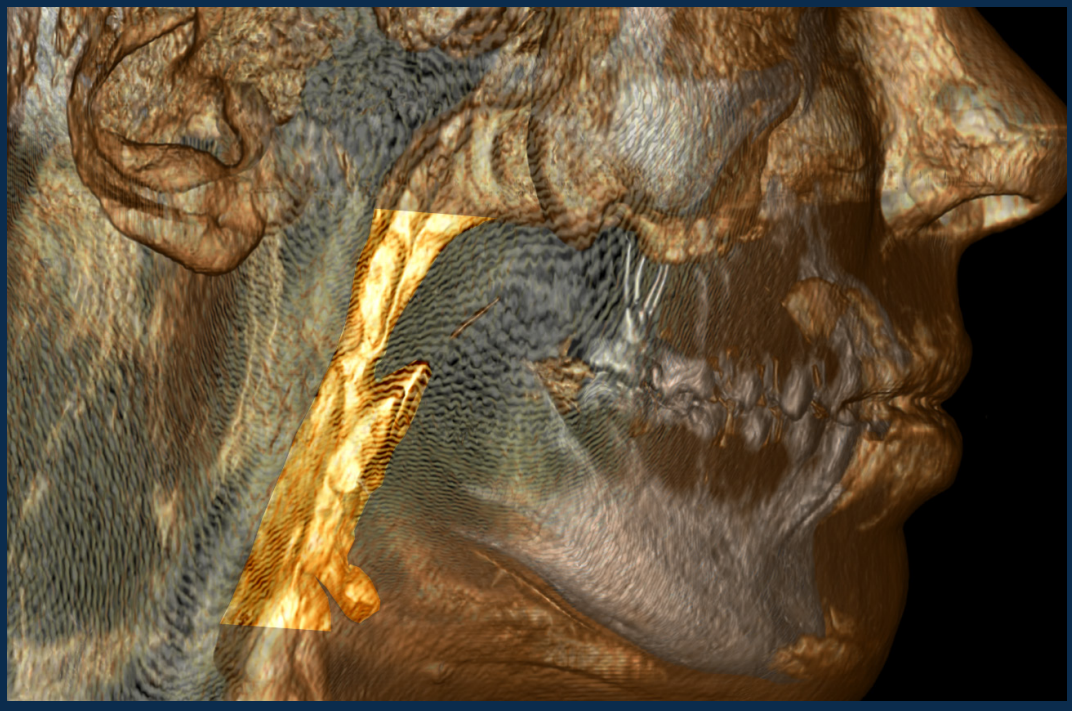
Publication date
2024
Document Version
Final published version

THE ROLE OF UPPER AIRWAY MORPHOLOGY IN OBSTRUCTIVE SLEEP APNEA



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ISBN: 978-94-6419-984-0

Publication of this thesis was financially supported by:

Academisch Centrum Tandheelkunde Amsterdam

De Nederlandse Vereniging voor Gnathologie en Prothetische Tandheelkunde; https://www.nvgpt.nl

SomnoMed; https://www.apneupagina.nl

De Nederlandse Vereniging voor Tandheelkundige Slaapgeneeskunde; https://www.nvts.nl

All Dent; https://alldent.nl

QR Srl, Verona, Italy; https://www.newtom.it

Oral Radiology Foundation Amsterdam

Cover concept: Xiaoxin Shi
Cover: Ilse Modder – www.ilsemodder.nl
Lay-out: Ilse Modder – www.ilsemodder.nl
Printed by: Gildeprint – www.gildeprint.nl

The role of upper airway morphology in obstructive sleep apnea

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 Agnietenkapel
op maandag 22 januari 2024, te 14.00 uur

door Xiaoxin Shi
geboren te Shandong

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Chapter 1

General introduction

Obstructive sleep apnea (OSA)

OSA is a condition characterized by repetitive complete and/or partial obstructions of the upper airway that are often related to oxygen desaturations and arousals from sleep [1]. The prevalence of OSA is estimated to be 14% in men and 5% in women in the general adult population [2]. Excessive daytime sleepiness, fatigue, impaired quality of life, lacking concentration, and loud snoring reported by the patient's bed partner are frequently reported complaints [3,4]. Furthermore, patients with untreated OSA are at increased risk of hypertension, stroke, heart failure, diabetes, and involvement in traffic and work-related accidents [5-9]. Therefore, ineffective treatment of OSA has severe consequences and is associated with enormous costs, both for the individual and for society.

Diagnosis

The diagnosis of OSA relies on the combination of signs, symptoms, and objective assessment of obstructive respiratory events. The gold standard for objectively assessing respiration during sleep is full-night polysomnography (PSG) [10]. A PSG recording often requires channels of electroencephalogram (EEG), electrooculogram (EOG), chin and limb electromyogram (EMG), airflow, arterial oxygen saturation (oximetry), respiratory effort (thoracic and abdominal breathing movements), heart rate or electrocardiography (ECG), and body position [11].

Currently, the most commonly used indicator of OSA severity is the number of respiratory events (apneas and/or hypopneas) per hour of sleep, viz., apnea-hypopnea index (AHI). Based on the American Academy of Sleep Medicine (AASM) criteria [1], apnea in adults is scored when there is a drop in the peak signal excursion by ≥ 90% of pre-event baseline for ≥ 10 seconds. Hypopnea in adults is scored when the peak signal excursions drop by ≥ 30% of pre-event baseline for ≥ 10 seconds in association with either ≥ 3% arterial oxygen desaturation or an arousal. An adult showing an AHI ≥ 15 events/h, or an AHI ≥ 5 events/h accompanied by one or more of the symptoms such as excessive daytime sleepiness, fatigue, or impaired cognition is diagnosed with OSA [1]. OSA severity for adults is classified as mild (5 ≤ AHI < 15 events/h), moderate (15 ≤ AHI ≤ 30 events/h), and severe (AHI > 30 events/h) [1].

Pathogenesis

The pathogenesis of OSA is multi-factorial, involving a complex interaction of both anatomical and non-anatomical factors, which remains incompletely understood [12]. In recent years, four main pathophysiological factors of OSA pathogenesis have been characterized, which include the anatomical factor of impaired upper airway morphology, and three non-anatomical factors of ineffective pharyngeal dilator muscle function, low arousal threshold, and unstable respiratory control (i.e., high loop gain) [13,14]. While the impaired upper airway morphology is a key determinant of OSA for most patients with OSA [15,16], its detailed role in the pathogenesis and treatment of OSA is still unclear. In this thesis, we therefore mainly focused on the role of upper airway morphology in the pathogenesis and treatment of OSA.

The upper airway is a collapsible tube, and the dimensions of the upper airway, as reflected by the volume, length, and size and shape of the cross-sectional area of the upper airway, are related to the propensity of upper airway collapse [17-19]. By comparing these variables together, a systematic review [20] indicated that a smaller minimal cross-sectional area (CSAmin) of the upper airway is the most relevant variable that is related to the pathogenesis of OSA. On the other hand, other variables may play an important role in the underlying mechanisms of different OSA phenotypes. For example, the shape of CSAmin of the upper airway (calculated as the ratio of the anteroposterior dimension to the lateral dimension at the location of the CSAmin) has been suggested to be related to the pathogenesis of positional OSA [21].

From an anatomical perspective, the upper airway is surrounded by soft tissue structures which are enclosed by maxillomandibular bony structures. As the upper airway lacks rigid support, both the skeletal restrictions (e.g., a smaller maxilla and mandible) and enlarged soft tissues (e.g., enlarged tongue and soft palatal volume) can result in impaired upper airway morphology [22]. Particularly, the anatomical balance, calculated as the ratio of tongue size to maxillomandibular enclosure size, has been increasingly recognized as an important determinant in the upper airway collapse as it synthesizes the effects of both soft and hard tissues and is related to the tissue pressure surrounding the upper airway [23-25].

Cone beam computed tomography (CBCT) is a commonly used imaging technique that can provide 3-dimensional anatomical data on the upper airway dimensions and its surrounding structures [26,27]. Compared to magnetic resonance imaging (MRI), another commonly used 3-dimensional imaging technique, CBCT is inferior

in discriminating between various soft-tissue structures [28]. However, CBCT is able to provide high resolution contrast between soft tissues, hard tissues, and airway space, which is widely used in assessing the upper airway morphology in the field of OSA [26,29]. Furthermore, CBCT is less expensive and more available than MRI. Besides, the image quality CBCT provides is relatively comparable to that obtained with traditional CT but has advantages in lower radiation exposure and cost [30,31]. In this thesis, we used CBCT to investigate the upper airway morphology.

Clinical phenotypes

OSA is a complex and heterogeneous disease, which challenges the personalized and precision medicine in this field [32]. To decrease the complex heterogeneity of OSA, patients with OSA can be classified to smaller and more homogeneous phenotypes according to disease characteristics [33]. By phenotyping, a better understanding of the pathogenesis and a more specific treatment strategy can be expected [34]. In this thesis, we have investigated the role of the upper airway morphology in the pathogenesis and treatment of OSA phenotypes classified by positional dependency, race, and specific craniofacial abnormalities.

Positional OSA

A striking feature of sleep-related obstructive respiratory events is that they are most severe and frequent in the supine position [35]. More than half of all patients with OSA can be classified as having positional OSA (POSA), which is defined as the AHI in the supine position being greater than twice the AHI in non-supine positions [36-38]. Although the POSA group forms a distinct clinical classification and goes with specific treatment recommendations, the underlying mechanism of this phenotype is not well understood [35]. Existing evidence suggests that the differential pathogenesis between POSA and non-POSA (NPOSA) is partly attributable to upper airway morphology [21,39]. However, in previous studies, the NPOSA group usually had more severe OSA compared to the POSA group, which may confound the findings. Therefore, the aim of **Chapter 2** was to compare anatomical balance and shape of the upper airway in the supine position between adults with POSA and adults with NPOSA.

Race

It is suggested that the pathogenesis of OSA varies between different races [40]. Studies have indicated that, when the OSA severity is similar, Caucasian adults with OSA are more overweight whereas Asian adults with OSA appear to show more severe skeletal restrictions (e.g., a smaller maxilla and mandible, and retrognathia)

[41-43]. However, the anatomical balance of the upper airway may be similar between the two races, and race has therefore probably a limited role in the anatomical determinants of upper airway collapse. To the best of our knowledge, only a few studies have conducted a direct inter-race comparison of the anatomical balance of the upper airway, and the results are inconclusive [42,43]. The different results could be related to many factors, such as different baseline characteristics, different imaging techniques, and different definitions of anatomical balance being used. Hence, studies that compare the anatomical balance of the upper airway between races are still needed. Therefore, the aim of **Chapter 3** was to compare the anatomical balance of the upper airway between Dutch and Chinese patients with OSA.

Craniofacial abnormalities

Common craniofacial abnormalities related to the development of OSA include a backwards-positioned mandible, a smaller maxilla, and a longer lower face height [44]. Individuals with Class II high-angle malocclusion have both mandibular retrognathia and mandibular vertical excess (longer lower face height) [45], with a smaller upper airway and a higher risk for developing OSA compared to individuals with normal occlusion and craniofacial structures [44]. While orthodontic premolar extractions treatment is typically used to correct dental malocclusion, it has little effect on mandibular vertical excess [46]. Studies have suggested that molar intrusion with skeletal anchorage (e.g., miniscrew-assisted) may cause the counterclockwise rotation of the mandible in patients with mandibular vertical excess [47-50], which may subsequently increase the upper airway dimensions via the lingual musculature (e.g., genioglossus muscle). However, to the best of our knowledge, studies on the effects of this treatment on mandibular position and upper airway dimensions in patients with Class II high-angle malocclusion are lacking. Therefore, in **Chapter 4**, we aimed to investigate the changes in upper airway dimensions and in mandibular position after miniscrew-assisted treatment with premolar extractions in adult patients with Class II high-angle malocclusion.

Treatment of OSA

Continuous positive airway pressure (CPAP) acts as a pneumatic pressure splint to prevent the collapse of the upper airway during sleep, which is regarded as the gold standard in the treatment of OSA [51]. However, due to the adverse effects and the cumbersome nature of CPAP, the adherence of patients to CPAP is low [52]. Other commonly used treatment modalities have therefore been developed, including treatment related to lifestyle changes (e.g., weight loss through diet and exercise,

sleep hygiene advice, and avoidance of alcohol), positional therapy, upper airway surgery, and mandibular advancement devices (MADs) [10]. Compared to other treatment options, MADs are easy to use, non-invasive, less expensive, and have similar treatment effects as CPAP in mild to moderate cases [53,54]. Therefore, MAD therapy is recommended as a primary treatment option in patients with mild and moderate OSA, and in patients with severe OSA who refuse or are unable to tolerate CPAP therapy [10,55,56]. The working mechanism of MAD is related to the increase of upper airway space by advancing the mandible and its attached soft tissues [57]. In this thesis, we mainly focused on MAD therapy.

MAD design

MADs can be categorized into two groups: customized and non-customized devices (e.g., thermoplastic material with boil-and-bite). In recent years, the customized type is increasingly recommended, as this type usually has a higher efficacy than the non-customized type [56,58]. There is a large variety of available customized MADs and among these, two types of MADs are commonly used: the Herbst appliance (MAD-H) and the SomnoDent appliance (MAD-S) (**Fig. 1**). They are both bi-block titratable MADs but differ predominantly in the freedom of vertical opening: the MAD-H only allows limited vertical opening, while the MAD-S allows free vertical opening of the mandible during sleep. The vertical opening of the MAD is suggested to compromise the treatment efficacy [59,60]. However, the effects of MADs with different freedom of mandibular vertical opening on OSA have not yet been determined in a randomized controlled trial (RCT). Therefore, the aim of **Chapter 5** was to compare the effects of MAD-H and MAD-S on respiratory parameters and upper airway dimensions in patients with mild to moderate OSA in an RCT.

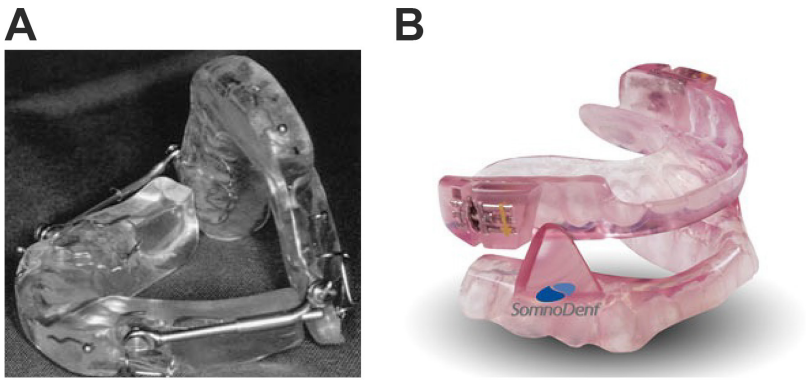

Fig. 1 Mandibular advancement devices (MADs). **A.** MAD-H (Herbst appliance; 4Dental labs, Amsterdam, the Netherlands). **B.** MAD-S (SomnoDent appliance; SomnoDent Flex, SomnoMed, Sydney, Australia)

MAD response

A major shortcoming of MAD therapy is the variable and unpredictable treatment efficacy, with approximately 50% non-responders [61,62]. However, the mechanism underlying different responses is not clear [56]. Therefore, there is an ongoing clinical interest in understanding the underlying mechanisms of inter-individual variability in response to MAD therapy. According to previous studies, the effects of MADs on upper airway dimensions may differ between individuals [63,64]. Therefore, the aim of **Chapter 6** was to compare the effects of MAD therapy on the upper airway dimensions between responders and non-responders with mild to moderate OSA.

General aim and outline of this thesis

The overall aim of this thesis was to evaluate the role of upper airway morphology in the pathogenesis and treatment of OSA. Specifically, the objectives were:

1. to give a general introduction to this thesis (**chapter 1**).
2. to compare the anatomical balance and shape of the upper airway in the supine position between adults with POSA and adults with NPOSA (**chapter 2**).
3. to compare the anatomical balance of the upper airway between Dutch and Chinese patients with OSA (**chapter 3**).
4. to investigate the changes in upper airway dimensions and mandibular position after miniscrew-assisted treatment with premolar extractions in adult patients with Class II high-angle malocclusion (**chapter 4**).
5. to compare the effects of MAD-H (allowing limited vertical opening) and MAD-S (allowing free vertical opening) on respiratory parameters and upper airway dimensions in patients with mild to moderate OSA in an RCT (**chapter 5**).
6. to compare the effects of MAD therapy on upper airway dimensions between responders and non-responders with mild to moderate OSA (**chapter 6**).
7. to provide a general discussion, focusing on methodological aspects, main research outcomes, clinical implications, and suggestions for future research (**chapter 7**).
8. to present a summary of this thesis in English, Dutch, and Chinese (**chapter 8-10**).

References

1. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF (2012) Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events: deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. Journal of clinical sleep medicine 8 (5):597-619
2. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM (2013) Increased prevalence of sleep-disordered breathing in adults. American journal of epidemiology 177 (9):1006-1014. doi:10.1093/aje/kws342
3. Gottlieb DJ, Whitney CW, Bonekat WH, Iber C, James GD, Lebowitz M, Nieto FJ, Rosenberg CE (1999) Relation of sleepiness to respiratory disturbance index: the Sleep Heart Health Study. American journal of respiratory and critical care medicine 159 (2):502-507
4. Chervin RD (2000) Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea. Chest 118 (2):372-379. doi:10.1378/chest.118.2.372
5. Peppard PE, Young T, Palta M, Skatrud J (2000) Prospective study of the association between sleep-disordered breathing and hypertension. New England Journal of Medicine 342 (19):1378-1384
6. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M (2010) Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation 122 (4):352-360
7. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM (2010) Obstructive sleep apnea–hypopnea and incident stroke: the sleep heart health study. American journal of respiratory and critical care medicine 182 (2):269-277
8. Kendzerska T, Gershon AS, Hawker G, Tomlinson G, Leung RS (2014) Obstructive sleep apnea and incident diabetes. A historical cohort study. American journal of respiratory and critical care medicine 190 (2):218-225
9. Luzzi V, Mazur M, Guaragna M, Di Carlo G, Cotticelli L, Magliulo G, Marasca B, Pirro V, Di Giorgio G, Ndokaj A, Pasqualetti P, Simonelli I, Martini A, Pietrafesa E, Polimeni A (2022) Correlations of Obstructive Sleep Apnea Syndrome and Daytime Sleepiness with the Risk of Car Accidents in Adult Working Population: A Systematic Review and Meta-Analysis with a Gender-Based Approach. Journal of clinical medicine 11 (14). doi:10.3390/jcm11143971
10. Epstein LJ, Kristo D, Strollo PJ, Jr., Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM, Weinstein MD (2009) Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 5 (3):263-276
11. Kushida CA, Littner MR, Morgenthaler T, Alessi CA, Bailey D, Coleman Jr J, Friedman L, Hirshkowitz M, Kapen S, Kramer M (2005) Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep 28 (4):499-523
12. White DP (2006) The pathogenesis of obstructive sleep apnea: advances in the past 100 years. American journal of respiratory cell and molecular biology 34 (1):1-6
13. Osman AM, Carter SG, Carberry JC, Eckert DJ (2018) Obstructive sleep apnea: current perspectives. Nature and science of sleep 10:21
14. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A (2013) Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. American journal of respiratory and critical care medicine 188 (8):996-1004
15. Carberry JC, Amatoury J, Eckert DJ (2018) Personalized management approach for OSA. Chest 153 (3):744-755
16. Eckert DJ, Malhotra A (2008) Pathophysiology of adult obstructive sleep apnea. Proceedings of the American thoracic society 5 (2):144-153
17. Abramson ZR, Susarla S, Tagoni JR, Kaban L (2010) Three-dimensional computed tomographic analysis of airway anatomy. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons 68 (2):363-371. doi:10.1016/j.joms.2009.09.086
18. Ogawa T, Enciso R, Shintaku WH, Clark GT (2007) Evaluation of cross-section airway configuration of obstructive sleep apnea. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics 103 (1):102-108. doi:10.1016/j.tripleo.2006.06.008
19. Schwab RJ, Gupta KB, Gefter WB, Metzger LJ, Hoffman EA, Pack AI (1995) Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. Am J Respir Crit Care Med 152 (5 Pt 1):1673-1689. doi:10.1164/ajrccm.152.5.7582313
20. Chen H, Aarab G, de Ruiter MH, de Lange J, Lobbezoo F, van der Stelt PF (2016) Three-dimensional imaging of the upper airway anatomy in obstructive sleep apnea: a systematic review. Sleep medicine 21:19-27
21. Pevernagie DA, Stanson A, Sheedy 2nd P, Daniels BK, Shepard Jr JW (1995) Effects of body position on the

upper airway of patients with obstructive sleep apnea. American journal of respiratory and critical care medicine 152 (1):179-185
22. Lee RW, Sutherland K, Cistulli PA (2010) Craniofacial morphology in obstructive sleep apnea: a review. Clinical Pulmonary Medicine 17 (4):189-195
23. Tsuiki S, Isono S, Ishikawa T, Yamashiro Y, Tatsumi K, Nishino T (2008) Anatomical Balance of the Upper Airway and Obstructive Sleep Apnea. Anesthesiology 108 (6):1009-1015. doi:10.1097/ALN.0b013e318173f103
24. Iida-Kondo C, Yoshino N, Kurabayashi T, Mataki S, Hasegawa M, Kurosaki N (2006) Comparison of tongue volume/oral cavity volume ratio between obstructive sleep apnea syndrome patients and normal adults using magnetic resonance imaging. Journal of medical and dental sciences 53 (2):119-126
25. Sutherland K, Almeida FR, de Chazal P, Cistulli PA (2018) Prediction in obstructive sleep apnoea: diagnosis, comorbidity risk, and treatment outcomes. Expert Review of Respiratory Medicine 12 (4):293-307
26. Chen H, Van Eijnatten M, Aarab G, Forouzanfar T, De Lange J, Van Der Stelt P, Lobbezoo F, Wolff J (2018) Accuracy of MDCT and CBCT in three-dimensional evaluation of the oropharynx morphology. European journal of orthodontics 40 (1):58-64
27. Chen H, Aarab G, Parsa A, de Lange J, van der Stelt PF, Lobbezoo F (2016) Reliability of three-dimensional measurements of the upper airway on cone beam computed tomography images. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 122 (1):104-110
28. Schwab RJ (1998) Upper airway imaging. Clinics in chest medicine 19 (1):33-54. doi:10.1016/s0272-5231(05)70430-5
29. Guijarro-Martínez R, Swennen GR (2011) Cone-beam computerized tomography imaging and analysis of the upper airway: a systematic review of the literature. International journal of oral and maxillofacial surgery 40 (11):1227-1237. doi:10.1016/j.ijom.2011.06.017
30. Palomo JM, Kau CH, Palomo LB, Hans MG (2006) Three-dimensional cone beam computerized tomography in dentistry. Dentistry today 25 (11):130
31. Suomalainen A, Kiljunen T, Kaser Y, Peltola J, Kortesniemi M (2009) Dosimetry and image quality of four dental cone beam computed tomography scanners compared with multislice computed tomography scanners. Dentomaxillofacial Radiology 38 (6):367-378
32. Malhotra A, Mesarwi O, Pepin JL, Owens RL (2020) Endotypes and phenotypes in obstructive sleep apnea. Curr Opin Pulm Med 26 (6):609-614. doi:10.1097/mcp.0000000000000724
33. Zinchuk AV, Gentry MJ, Concato J, Yaggi HK (2017) Phenotypes in obstructive sleep apnea: A definition, examples and evolution of approaches. Sleep Med Rev 35:113-123. doi:10.1016/j.smrv.2016.10.002
34. Zinchuk A, Yaggi HK (2020) Phenotypic Subtypes of OSA: A Challenge and Opportunity for Precision Medicine. Chest 157 (2):403-420. doi:10.1016/j.chest.2019.09.002
35. Joosten SA, O'Driscoll DM, Berger PJ, Hamilton GS (2014) Supine position related obstructive sleep apnea in adults: pathogenesis and treatment. Sleep medicine reviews 18 (1):7-17
36. Sunwoo WS, Hong S-L, Kim S-W, Park SJ, Han DH, Kim J-W, Lee CH, Rhee C-S (2012) Association between positional dependency and obstruction site in obstructive sleep apnea syndrome. Clinical and experimental otorhinolaryngology 5 (4):218
37. Oksenberg A, Arons E, Radwan H, Silverberg DS (1997) Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic and multiple sleep latency test data. Chest 112 (3):629-639
38. Teerapraipruk B, Chirakalwasan N, Simon R, Hirunwiwatkul P, Jaimchariyatam N, Desudchit T, Charakorn N, Wanlapakorn C (2012) Clinical and polysomnographic data of positional sleep apnea and its predictors. Sleep and Breathing 16 (4):1167-1172
39. Saigusa H, Suzuki M, Higurashi N, Kodera K (2009) Three-dimensional Morphological Analyses of Positional Dependence in Patients with Obstructive Sleep Apnea Syndrome. Anesthesiology 110 (4):885-890. doi:10.1097/ALN.0b013e31819b5d57
40. Hnin K, Mukherjee S, Antic NA, Catcheside P, Chai-Coetzer CL, McEvoy D, Vakulin A (2018) The impact of ethnicity on the prevalence and severity of obstructive sleep apnea. Sleep Med Rev 41:78-86. doi:10.1016/j.smrv.2018.01.003
41. Liu Y, Lowe AA, Zeng X, Fu M, Fleetham JA (2000) Cephalometric comparisons between Chinese and Caucasian patients with obstructive sleep apnea. American Journal of Orthodontics & Dentofacial Orthopedics 117 (4):479-485
42. Lee RW, Vasudavan S, Hui DS, Prvan T, Petocz P, Darendeliler MA, Cistulli PA (2010) Differences in craniofacial structures and obesity in Caucasian and Chinese patients with obstructive sleep apnea. Sleep 33 (8):1075-1080
43. Schorr F, Kayamori F, Hirata RP, Danzi-Soares NJ, Gebrim EM, Moriya HT, Malhotra A, Lorenzi-Filho G, Genta PR (2016) Different craniofacial characteristics predict upper airway collapsibility in Japanese-Brazilian and white men. Chest 149 (3):737-746
44. Neelapu BC, Kharbanda OP, Sardana HK, Balachandran R, Sardana V, Kapoor P, Gupta A, Vasamsetti

S (2017) Craniofacial and upper airway morphology in adult obstructive sleep apnea patients: A systematic review and meta-analysis of cephalometric studies. Sleep Med Rev 31:79-90. doi:10.1016/j.smrv.2016.01.007
45. Moyers RE, Riolo ML, Guire KE, Wainright RL, Bookstein FL (1980) Differential diagnosis of Class II malocclusions: Part 1. Facial types associated with Class II malocclusions. American journal of orthodontics 78 (5):477-494
46. Kuroda S, Katayama A, Takano-Yamamoto T (2004) Severe anterior open-bite case treated using titanium screw anchorage. The Angle orthodontist 74 (4):558-567. doi:10.1043/0003-3219(2004)074<0558:saoctu>2.0.co;2
47. Kuroda S, Sakai Y, Tamamura N, Deguchi T, Takano-Yamamoto T (2007) Treatment of severe anterior open bite with skeletal anchorage in adults: Comparison with orthognathic surgery outcomes. American Journal of Orthodontics and Dentofacial Orthopedics 132 (5):599-605. doi:https://doi.org/10.1016/j.ajodo.2005.11.046
48. Sugawara J, Baik UB, Umemori M, Takahashi I, Nagasaka H, Kawamura H, Mitani H (2002) Treatment and posttreatment dentoalveolar changes following intrusion of mandibular molars with application of a skeletal anchorage system (SAS) for open bite correction. The International journal of adult orthodontics and orthognathic surgery 17 (4):243-253
49. Sherwood KH, Burch JG, Thompson WJ (2002) Closing anterior open bites by intruding molars with titanium miniplate anchorage. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics 122 (6):593-600. doi:10.1067/mod.2002.128641
50. Erverdi N, Keles A, Nanda R (2004) The use of skeletal anchorage in open bite treatment: a cephalometric evaluation. The Angle orthodontist 74 (3):381-390. doi:10.1043/0003-3219(2004)074<0381:tuosai>2.0.co;2
51. Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ (2006) Continuous positive airways pressure for obstructive sleep apnoea in adults. The Cochrane database of systematic reviews (3):Cd001106. doi:10.1002/14651858.CD001106.pub3
52. Richard W, Venker J, den Herder C, Kox D, van den Berg B, Laman M, van Tinteren H, de Vries N (2007) Acceptance and long-term compliance of nCPAP in obstructive sleep apnea. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 264 (9):1081-1086. doi:10.1007/s00405-007-0311-3
53. Aarab G, Lobbezoo F, Hamburger HL, Naeije M (2011) Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial. Respiration 81 (5):411-419
54. Randerath W, Verbraecken J, de Raaff CAL, Hedner J, Herkenrath S, Hohenhorst W, Jakob T, Marrone O, Marklund M, McNicholas WT, Morgan RL, Pepin JL, Schiza S, Skoetz N, Smyth D, Steier J, Tonia T, Trzepizur W, van Mechelen PH, Wijkstra P (2021) European Respiratory Society guideline on non-CPAP therapies for obstructive sleep apnoea. European respiratory review : an official journal of the European Respiratory Society 30 (162). doi:10.1183/16000617.0200-2021
55. Sharples LD, Clutterbuck-James AL, Glover MJ, Bennett MS, Chadwick R, Pittman MA, Quinnell TG (2016) Meta-analysis of randomised controlled trials of oral mandibular advancement devices and continuous positive airway pressure for obstructive sleep apnoea-hypopnoea. Sleep Med Rev 27:108-124. doi:10.1016/j.smrv.2015.05.003
56. Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, Chervin RD (2015) Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015: an American Academy of Sleep Medicine and American Academy of Dental Sleep Medicine clinical practice guideline. Journal of clinical sleep medicine 11 (7):773-827
57. Sutherland K, Vanderveken OM, Tsuda H, Marklund M, Gagnadoux F, Kushida CA, Cistulli PA (2014) Oral appliance treatment for obstructive sleep apnea: an update. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 10 (2):215-227. doi:10.5664/jcsm.3460
58. Venema JAU, Rosenmöller BR, De Vries N, de Lange J, Aarab G, Lobbezoo F, Hoekema A (2021) Mandibular advancement device design: A systematic review on outcomes in obstructive sleep apnea treatment. Sleep medicine reviews 60:101557
59. Mayoral P, Lagravère M, Míguez-Contreras M, Garcia M (2019) Antero-posterior mandibular position at different vertical levels for mandibular advancing device design. BMC Oral Health 19 (1):1-8
60. Nikolopoulou M, Naeije M, Aarab G, Hamburger H, Visscher C, Lobbezoo F (2011) The effect of raising the bite without mandibular protrusion on obstructive sleep apnoea. Journal of Oral Rehabilitation 38 (9):643-647
61. Sutherland K, Chan ASL, Ngiam J, Dalci O, Darendeliler MA, Cistulli PA (2018) Awake Multimodal Phenotyping for Prediction of Oral Appliance Treatment Outcome. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 14 (11):1879-1887. doi:10.5664/

jcsm.7484
62. Brown EC, Jugé L, Knapman FL, Burke PGR, Ngiam J, Sutherland K, Butler JE, Eckert DJ, Cistulli PA, Bilston LE (2021) Mandibular advancement splint response is associated with the pterygomandibular raphe. Sleep 44 (4). doi:10.1093/sleep/zsaa222
63. Gao X, Otsuka R, Ono T, Honda E-i, Sasaki T, Kuroda T (2004) Effect of titrated mandibular advancement and jaw opening on the upper airway in nonapneic men: a magnetic resonance imaging and cephalometric study. American journal of orthodontics and dentofacial orthopedics 125 (2):191-199
64. De Backer JW, Vanderveken OM, Vos WG, Devolder A, Verhulst SL, Verbraecken JA, Parizel PM, Braem MJ, Van de Heyning PH, De Backer WA (2007) Functional imaging using computational fluid dynamics to predict treatment success of mandibular advancement devices in sleep-disordered breathing. Journal of biomechanics 40 (16):3708-3714. doi:10.1016/j.jbiomech.2007.06.022

Chapter 2

Upper airway morphology in adults with positional obstructive sleep apnea

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Published as: Shi, X., Sutherland, K., Lobbezoo, F., Berkhout, E., de Lange, J., Cistulli, P., Darendeliler, M., Dalci, O., & Aarab, G. (2023). Upper airway morphology in adults with positional obstructive sleep apnea. Sleep & breathing = Schlaf & Atmung, 10.1007/s11325-023-02879-0. Advance online publication. https://doi.org/10.1007/s11325-023-02879-0

Abstract

Purpose

To compare the anatomical balance and shape of the upper airway in the supine position between adults with positional obstructive sleep apnea (POSA) and adults with non-positional OSA (NPOSA).

Methods

Adults diagnosed with OSA (apnea-hypopnea index (AHI) > 10 events/h) were assessed for eligibility. POSA was defined as the supine AHI more than twice the AHI in non-supine positions; otherwise, patients were classified as NPOSA. Cone beam computed tomography (CBCT) imaging was performed for every participant while awake in the supine position. The anatomical balance was calculated as the ratio of the tongue size to the maxillomandibular enclosure size. The upper airway shape was calculated as the ratio of the anteroposterior dimension to the lateral dimension at the location of the minimal cross-sectional area of the upper airway (CSAmin-shape).

Results

Of 47 participants (28 males, median age [interquartile range] 56 [46 to 63] years, median AHI 27.8 [15.0 to 33.8]), 34 participants were classified as having POSA (72%). The POSA group tended to have a higher proportion of males and a lower AHI than the NPOSA group (P = 0.07 and 0.07, respectively). After controlling for both sex and AHI, the anatomical balance and CSAmin-shape were not significantly different between both groups (P = 0.18 and 0.73, respectively).

Conclusion

Adults with POSA and adults with NPOSA have similar anatomical balance and shape of their upper airway in the supine position.

Keywords

Positional obstructive sleep apnea, Cone beam computed tomography, Anatomical balance of the upper airway, Upper airway shape

1. Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent complete (i.e., apnea) and partial (i.e., hypopnea) obstructions of the upper airway [1]. These respiratory events are most frequent and severe in the supine position [2]. It has been estimated that more than 50% of patients with OSA suffer from positional OSA (POSA) [3,4]. Despite having well defined clinical features and specific treatment recommendations, the underlying mechanisms for POSA are not clear [5]. Evidence suggests that the differential pathogenesis between POSA and non-POSA (NPOSA) is partly attributable to anatomical factors, such as upper airway morphology [5,6]. Some anatomical OSA treatments (e.g., upper airway surgery and oral appliance therapy) also show different treatment effects between patients with POSA and NPOSA [7,8].

The upper airway is surrounded by soft tissue structures enclosed by maxillomandibular bony structures. Research suggests that both soft and hard craniofacial structures are related to upper airway shape and size, and these affect the severity of OSA [9]. The ratio of tongue size to maxillomandibular enclosure size – termed 'anatomical balance' – is an important risk factor in OSA, particularly in the supine position [10,11]. Anatomical imbalance (i.e., an enlarged tongue size to maxillomandibular enclosure size ratio) indicates higher tissue pressure surrounding the upper airway and decreased upper airway size [12]. However, only a few studies have compared craniofacial structures between POSA and NPOSA groups. Two studies have suggested that patients with POSA may have a smaller lower facial height, more backward positioned mandible, and shorter soft palatal length than patients with NPOSA [13,14]. However, Saigusa et al. [14] found no significant difference in the anatomical balance of the upper airway between the POSA and NPOSA groups in their study. Thus, studies on the differences in craniofacial structures between both groups are still limited.

Furthermore, studies by Pevernagie et al. [6] and Jiao et al. [13] have suggested that patients with NPOSA have a more circular cross-sectional area of the upper airway compared to patients with POSA, which may explain the differential pathogenesis between the groups. However, in both studies, participants had relatively severe OSA, and patients with NPOSA had more severe OSA. By contrast, a study by Joosten et al. [15] found no significant difference between POSA and NPOSA in upper airway shape, but the sample size was small (each group had only eight subjects). Hence, the difference in upper airway shape between POSA and NPOSA is not clear [5]. Accordingly, a large-scale study across the spectrum of OSA severity is necessary to provide more evidence on the potential differences in upper airway shape between POSA and NPOSA and their effect on treatment outcome.

In the supine position, the exacerbation of obstructive respiratory events may be related to the collapse of the anterior wall of the upper airway due to the effect of gravity. Accordingly, we hypothesize that: (1) adults with POSA have a greater anatomical imbalance (i.e., a higher ratio of tongue size to maxillomandibular enclosure size) compared to adults with NPOSA, and therefore a greater tendency of upper airway collapse in the anteroposterior direction in the supine position; and (2) adults with POSA have a more elliptically shaped cross-sectional area (i.e., a smaller ratio of the anteroposterior dimension to the lateral dimension) compared to adults with NPOSA, and therefore a greater tendency of upper airway collapse in the anteroposterior direction in the supine position. Accordingly, this study aimed to compare the anatomical balance and shape of the upper airway between adults with POSA and adults with NPOSA in the supine position.

2. Material and methods

2.1 Overview

This study is part of a prospective study [16], in which adults with OSA (apnea-hypopnea index (AHI) > 10 events/h) were recruited for building a prediction model for oral appliance treatment outcomes. This study received ethical approval (Sydney Local Health District, Protocol No. X11-0134 & HREC/11/RPAH/192), and informed consent was obtained from all participants. This study was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR Trial ACTRN12611000409976).

2.2 Participants

Patients were recruited prospectively from sleep clinics associated with a tertiary teaching hospital in Sydney (Royal North Shore Hospital). The inclusion criteria were adults (> 18 years of age) diagnosed with OSA (AHI > 10 events/h) using in-laboratory polysomnography (PSG) who were willing to try oral appliance therapy. Exclusion criteria were limited to contraindications to oral appliance therapy (e.g., severe periodontal disease and an insufficient number of teeth). There were no upper limits on AHI or body mass index (BMI) for recruitment. Ethnicity was recorded using a self-reporting questionnaire, in which participants selected their ethnicity based on their culture, religion, skin color, and language from the following four ethnic groups: Asian, Native Hawaiian and Pacific Islanders, Hispanic and Latino, and White. Patients were classified as positional OSA (POSA) if their AHI in supine position (AHI-supine) was more than twice their AHI in non-supine positions (AHI-non-supine) [17]. If this criterion was not fulfilled, patients were classified as non-positional OSA (NPOSA).

2.3 CBCT acquisition

Every participant underwent a CBCT scan (NewTom 3G, QR systems, Italy) in the supine position while awake [16]. During the scanning process, patients were asked to bite gently in natural occlusion, lightly touch their teeth with their tongue, refrain from swallowing, and bring their lips into a relaxed position. The exposure settings were 110 kVp, 2-3 mA, and exposure time was 5–15 s. Voxel size was 0.36 mm or 0.42 mm, depending on the scan settings. A standardization of head position was performed after scanning. During this process, the palatal plane was adjusted to be parallel to the axial and sagittal planes and perpendicular to the coronal plane. CBCT datasets were saved as Digital Imaging and Communications in Medicine (DICOM) files.

2.4 Anatomical balance

3Diagnosys® software (v5.3.1, 3diemme, Cantu, Italy) was used to measure craniofacial structures, including the soft palate, tongue, hyoid, maxilla, mandible, and face height. The primary variable – the anatomical balance of the upper airway – was calculated as the ratio of the tongue size to maxillomandibular enclosure size in the mid-sagittal plane of the CBCT image. Tongue size was defined as the area enclosed by the point Hyoid (H), Menton (Me), the contour of the frontal teeth and the tongue, and the base of the epiglottis (**Fig. 1A**). Meanwhile, the maxillomandibular enclosure size was defined as the area enclosed by the point Hyoid (H), Menton (Me), the contour of the front teeth, the hard palate, the point posterior nasal spine (PNS), and the anterior boundary of the second and third cervical vertebra (**Fig. 1B**). The definitions for the secondary outcome variables, such as the soft palate, tongue, hyoid, maxilla, mandible, and face height, are illustrated in **Fig. 2**.

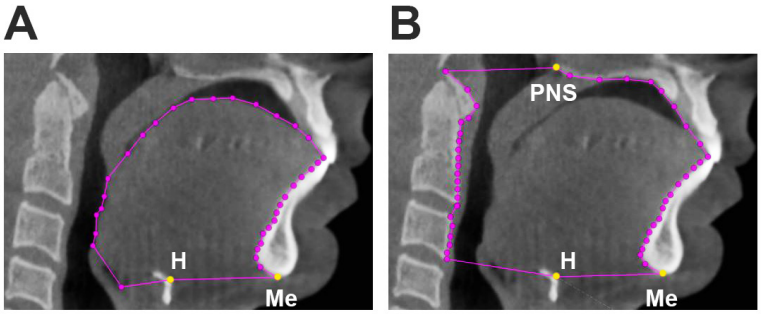

Fig. 1 Measurements of tongue size and maxillomandibular enclosure size using cone beam computed tomography (CBCT) imaging in the mid-sagittal plane. **A.** Tongue size: area enclosed by the point Hyoid (H), Menton (Me), the contour of the frontal teeth and tongue, and the base of the epiglottis. **B.** Maxillomandibular enclosure size: area enclosed by the point Hyoid (H), Menton (Me), the contour of the front teeth, the hard palate, point posterior nasal spine (PNS), and the anterior boundary of the second and third cervical vertebra

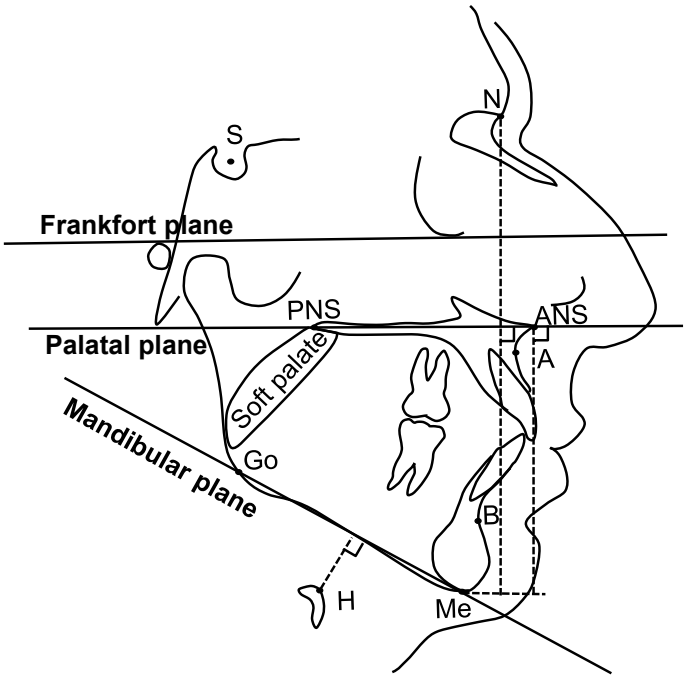

Fig. 2 Illustration of the secondary outcome variables of the craniofacial structures. Soft palate length (distance from PNS to the tip of the soft palate), Hyoid to MP plane (distance between H and Mandibular plane), SNA (angle between points A and S at N), Maxillary length (distance between ANS and PNS), SNB (angle between points B and S at N), Mandibular length (distance between Me and Go), Mandibular plane angle (angle between Frankfort plane and Mandibular plane), Face height (distance between N and Me), Lower face height (distance between ANS and Me). Landmarks: N = nasion, S = sella, ANS = anterior nasal spine, PNS = posterior nasal spine, Go = gonion, Me = menton, H = hyoidale, A = subspinale, B = supramentale

2.5 Upper airway shape

Upper airway shape and size were analyzed using CBCT images with Amira® software (v4.1, Visage Imaging Inc., Carlsbad, CA, USA). The superior boundary of the upper airway was the palatal plane; the inferior boundary was the horizontal plane (parallel to the palatal plane) across the base of the epiglottis (**Fig. 3A**). After applying the upper airway boundaries, the total upper airway volume (V) and the cross-sectional area (CSA) of each slice were calculated using the same software. The minimum CSA (CSAmin) was identified based on the CSA results. The anteroposterior dimension (A-P) and lateral dimension (Lat) of CSAmin were measured (**Fig. 3B**) on the specific slice where the CSAmin was located. The shape of CSAmin (CSAmin-shape) was calculated as the ratio of A-P to Lat; this was the primary outcome variable for representing the upper airway shape at the CSAmin location.

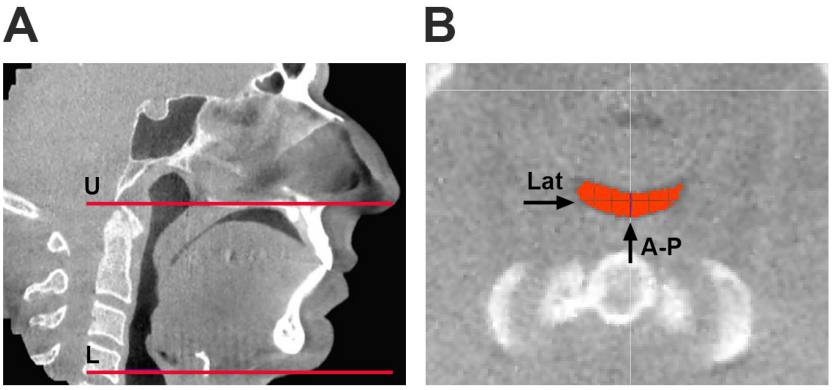

Fig. 3 Upper airway boundaries and measurements of the upper airway shape, using cone beam computed tomography (CBCT) imaging. **A.** The segmentation of the upper airway from the upper boundary (U) to the lower boundary (L) in the mid-sagittal plane. **B.** The measurement of the anterior-posterior dimension (A-P) and lateral dimension (Lat) of the minimum cross-sectional area of the upper airway (CSAmin) in the axial plane

2.6 Reliability of measurements

All upper airway variables were measured by an experienced examiner blinded to group membership. To determine the intra-observer reliability of the measurements, 15 CBCT scans were randomly selected and re-measured after three months of the original measurements.

The calculation of sample size for the reliability assessment was performed according to Walter et al. [18]. We assumed that our actual intra-observer reliability in the present study is at least 0.9, and a reliability of 0.6 or higher would be acceptable based on our previous study [19]. Therefore, the null hypothesis was defined as H0: $\rho 0 = 0.6$, and the alternative hypothesis was defined as H1: $\rho 1 = 0.9$, with a significance level of 0.05 and a power of 0.8. Based on this hypothesis, the proposed sample size was 15 patients [18].

2.7 Statistical Analysis

A Shapiro-Wilk test was used to test the normality of continuous data. An independent t test (for normally distributed variables), a Mann-Whitney U test (for non-normally distributed variables), and a Chi-squared test (or Fisher's exact test) (for nominal variables) were used to compare the baseline demographic characteristics and PSG parameters between the POSA and NPOSA groups.

An intraclass correlation coefficient (ICC) was performed to determine the intra-observer reliability of the measurements of anatomical variables. The anatomical

variables of upper airway morphology were compared between the POSA and NPOSA groups using analysis of covariance (ANCOVA). The baseline characteristics that were significantly different between both groups were treated as covariates. The significance level was set at 0.05, and statistical analyses were carried out using SPSS software (SPSS version 26, Chicago, IL, USA).

The effect sizes for primary outcome variables were calculated using the program G*power (version 3.1.9, Franz Faul, Universität Kiel, Germany).

3. Results

3.1 Participant's recruitment

A total of 60 patients were assessed for eligibility. Of these, 13 patients with incomplete information were excluded from the analysis: n = 2 with incomplete baseline demographic data, n = 5 with incomplete PSG data, and n = 6 with CBCT images that were distorted or/and lacked landmarks for the primary outcome variables. After exclusions, 47 patients were included in the analysis: 34 patients with POSA, and 13 patients with NPOSA.

3.2 Patient characteristics

The baseline demographic characteristics and respiratory and sleep parameters for POSA and NPOSA groups are provided in **Table 1**. There were no significant differences between the groups in age, sex, body mass index, neck circumference, waist circumference, and ethnicity (P = 0.07-0.88). For the respiratory variables, no significant differences were found in AHI and AHI-supine between both groups (P = 0.07 and 0.39, respectively); however, by definition, the AHI-non-supine was significantly higher in the NPOSA group compared to the POSA group (Z = -4.31, P < 0.01). For the sleep variables, there were no significant differences between the groups (P = 0.20-0.75). As the sex and AHI tended to have a significant difference between the groups (P = 0.07 and P = 0.07, respectively), these two variables were treated as covariates in the ANCOVA analyses.

3.3 Reliability of measurements

The intra-observer reliability was excellent for the primary variables (ICC = 0.91 for the anatomical balance, ICC = 0.97 for the CSAmin-shape) and secondary variables (ICC = 0.92-0.99) [20].

Table 1 Baseline demographic characteristics, respiratory and sleep parameters of the POSA and NPOSA groups

	POSA (*n* = 34)	NPOSA (*n* = 13)	Test statistic	*P*
Demographic characteristics				
Age (years)	55.5 (46.0-63.3)	60.0 (46.0-63.0)	-0.16 (Z)	0.88
Sex (male vs female)	23 vs 11	5 vs 8	3.33 (χ^2)	0.07
BMI (kg/m^2)	29.2 ± 5.1	30.1 ± 6.2	-0.52 (t)	0.61
Neck circumference (cm)	40.5 ± 3.3	39.0 ± 3.2	1.34 (t)	0.19
Waist circumference (cm)	102.0 ± 12.6	100.2 ± 14.0	0.43 (t)	0.67
Ethnicity (race 1 vs 2 vs 3 vs 4)	7 vs 1 vs 3 vs 23	1 vs 0 vs 0 vs 12	2.53 (FET)	0.58
Respiration				
AHI (events/h)	21.8 (13.7-30.8)	32.2 (21.7-39.9)	-1.82 (Z)	0.07
AHI-supine (events/h)	44.0 (24.0-64.1)	34.8 (20.1-56.9)	-0.86 (Z)	0.39
AHI-non-supine (events/h)	6.0 (3.0-13.5)	30.7 (23.3-34.4)	-4.31 (Z)	<0.01*
Sleep				
TST (min)	360.1 ± 45.0	330.8 ± 117.6	0.87 (t)	0.40
ST-supine (min)	165.0 ± 97.8	126.2 ± 75.5	1.29 (t)	0.20
ST-REM (%)[a]	15.8 ± 6.3	15.1 ± 7.3	0.32 (t)	0.75
ST-NREM (%)[b]	84.0 ± 5.2	84.9 ± 7.3	-0.43 (t)	0.67

Normally distributed data are shown as means ± standard deviations (SD); non-normally distributed data are presented as medians (interquartile range); *t*, independent t test; *Z*, Mann-Whitney U test; χ^2, Chi-squared test; *FET*, fisher's exact test

POSA, positional OSA; *NPOSA,* non-positional OSA; *BMI*, body mass index; *Ethnicity, race* 1 = Asian, race 2 = Native Hawaiian or Pacific Island, race 3 = Hispanic or Latino, race 4 = White; *AHI,* apnea–hypopnea index; *AHI-supine,* AHI in supine position; *AHI-non-supine,* AHI in positions other than supine position; *TST,* total sleep time; *ST-supine,* sleep time in the supine position; *ST-REM*, sleep time in rapid-eye-movement stage; *ST-NREM,* sleep time in non-rapid-eye-movement stage

[a]2 patients in the POSA group with incomplete REM data were excluded from the analysis

[b]5 patients in the POSA group with incomplete NREM data were excluded from the analysis

* Statistically significant

3.4 Anatomical balance

Table 2 provides the anatomical variables of the upper airway of the POSA and NPOSA groups. There was no significant difference between the groups for the primary outcome variable: the anatomical balance of the upper airway (F = 1.85, P = 0.18). The individual values of anatomical balance for both groups are shown in **Fig. 4A**. The effect size f of the anatomical balance comparison was 0.2 (partial η^2 = 0.04, ANCOVA). This can be qualified as being between small and medium. For the secondary outcome variables, there were no significant differences between the groups either (all P > 0.05).

Table 2 The anatomical variables of the upper airway of the POSA and NPOSA groups

	POSA (n = 34)	NPOSA (n = 13)	F^a (ANCOVA)	P
Primary outcome variable				
Anatomical balance ratio	0.7 ± 0.0	0.7 ± 0.0	1.85	0.18
Secondary outcome variables				
Maxillomandibular enclosure area (mm^2)	4666.7 ± 528.2	4403.4 ± 567.0	1.46	0.23
Tongue area (mm^2)	3294.6 ± 413.5	2985.4 ± 377.4	3.71	0.06
Soft palate length (mm)	38.7 ± 4.2	40.1 ± 4.5	0.25	0.62
Hyoid to mandibular plane (mm)	18.8 ± 6.1	16.2 ± 4.6	0.90	0.35
SNA (°) [b]	82.7 ± 3.2	81.5 ± 2.5	0.03	0.87
Maxillary length (mm)	55.1 ± 3.9	53.2 ± 3.2	1.30	0.26
SNB (°) [b]	78.6 ± 4.0	77.6 ± 3.1	0.01	0.92
Mandibular length (mm)	70.5 ± 4.6	69.2 ± 4.0	0.09	0.76
Mandibular plane angle (°)	24.3 ± 6.1	26.2 ± 4.5	0.59	0.45
Face height (mm) [b]	118.7 ± 6.0	116.5 ± 9.0	0.14	0.71
Lower face height (mm) [c]	65.9 ± 4.7	65.3 ± 5.3	0.13	0.72

Data are shown as means ± standard deviations
SNA, angle between sella, nasion, and subspinale (point A); *SNB,* angle between sella, nasion, and supramentale (point B)
[a]the sex and AHI were controlled as covariates for the comparisons
[b]3 patients in the POSA group with incomplete CBCT image were excluded from the analysis
[c]1 patient in the POSA group with incomplete CBCT image was excluded from the analysis

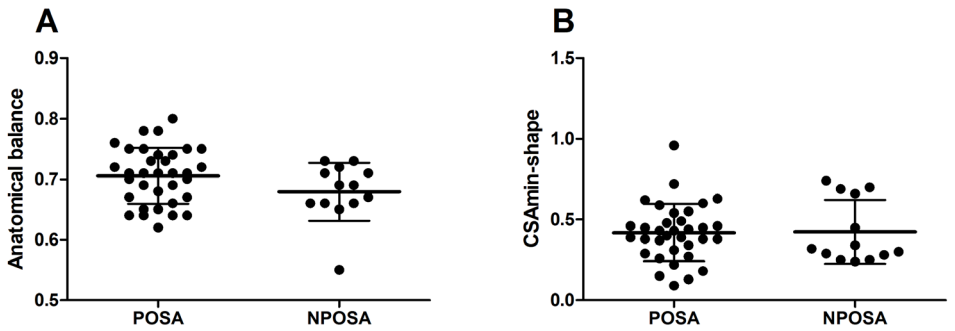

Fig. 4 Individual values (dot plots, means with standard deviations) of the anatomical balance and CSAmin-shape of the POSA group (n = 34) and NPOSA group (n = 13). **A.** Illustration of the anatomical balance of the upper airway. **B.** Illustration of the CSAmin-shape

3.5 Upper airway shape

The upper airway dimensional variables of the POSA and NPOSA groups are shown in **Table 3**. For the primary outcome variable, CSAmin-shape, there was no significant difference between the groups (F = 0.12, P = 0.73). The individual values of the CSAmin-shape of both groups are presented in **Fig. 4B**. The effect size f of

the CSAmin-shape comparison was 0.05 (partial η^2 = 0.003, ANCOVA), which can be qualified as small. For the secondary outcome variables, there were no significant differences between the groups either (P = 0.23-0.98).

Table 3 The upper airway dimensions of the POSA and NPOSA groups

	POSA (n = 34)	NPOSA (n = 13)	F^a (ANCOVA)	P
Primary outcome variable				
CSAmin-shape	0.4 ± 0.2	0.4 ± 0.2	0.12	0.73
Secondary outcome variables				
A-P (mm)	4.9 ± 2.0	5.1 ± 1.4	0.18	0.68
Lat (mm)	12.8 ± 4.5	13.1 ± 3.5	1.51	0.23
CSAmin size (mm^2)	60.2 ± 40.3	61.3 ± 20.1	0.48	0.49
L (mm)	66.6 ± 7.7	63.1 ± 8.1	0.63	0.43
V (cm^3)	12.8 ± 11.9	12.0 ± 4.1	0.00	0.98

Data are shown as means ± standard deviations
CSAmin, minimum cross-sectional area of the upper airway; *A-P,* anterior-posterior dimension of the CSAmin; *Lat,* lateral dimension of the CSAmin; *CSAmin-shape,* the ratio of A-P to Lat; *L,* upper airway length; *V,* upper airway volume
[a]the sex and AHI were controlled as covariates for the comparisons

4. Discussion

In the present study, we hypothesized that adults with POSA have a greater anatomical imbalance and a more elliptically shaped cross-sectional area of the upper airway in the supine position compared to adults with NPOSA. The results of this study showed no significant difference between both groups in these outcomes.

4.1 Anatomical balance of the upper airway

No significant difference in the anatomical balance between the POSA and NPOSA groups was found. The observed effect size of the anatomical balance comparison was small to medium [21]. Therefore, the clinical relevance of the difference in this variable between both groups is controversial. Consistent with our results, Saigusa et al.'s study [14] calculated the anatomical balance using three-dimensional structures' volume with magnetic resonance imaging (MRI) and found no significant difference between POSA and NPOSA either.

Regarding secondary variables, previous studies have indicated that patients with POSA show a larger ANB angle, smaller lower facial height, and shorter soft palate length compared to patients with NPOSA [13,14]. However, we found no significant

difference between both groups in those structures. Both previous studies' samples were predominantly of Asian ethnicity, so the different ethnic balance in our study sample (74% white) may explain the different findings in these structures.

4.2 Upper airway shape

The present study found no significant difference in CSAmin-shape between the POSA and NPOSA groups. Furthermore, the observed effect size of the CSAmin-shape comparison was small [21], indicating that the difference in CSAmin-shape between both groups is not clinically relevant. In contrast to our study results, a study by Pevernagie et al. [6] indicates that CSAmin-shape was more circular in the NPOSA group compared to the POSA group in the supine position. In their study, however, the NPOSA group had significantly higher AHI than the POSA group (83 vs. 31 events/h). Since it has been suggested that CSAmin-shape is related to AHI [22], the higher AHI in the NPOSA group could be a confounding factor in the comparison of CSAmin-shape, and it may explain the different results in comparison to our study. In line with our results, a study by Joosten et al. [15] suggested no significant difference in CSAmin-shape between both groups. Although their study had a small sample size (each group had eight subjects), our study confirmed their results with a larger sample. Therefore, it seems that upper airway shape is similar for POSA and NPOSA groups in the supine position, especially when their AHI severity is matched.

4.3 Implications

As upper airway morphology was not significantly different between the POSA and NPOSA groups in the present study, it may be hypothesized that non-anatomical factors account for the differences in pathogenesis between both groups. Joosten et al. [23] have shown that, turning from a supine to a lateral position, the muscular ability to stiffen and dilate the airway is more effective in the POSA group compared to the NPOSA group. The less effective muscle activities in the NPOSA group may be caused by greater vulnerability to muscle fatigue (due to the increased number of type II fibers) [24], poor muscle effectiveness (caused by excessive fat or muscle hypertrophy) [25], and disturbed coordination of the neural drives between upper airway and respiratory muscles [26,27]. Another study, undertaken by Joosten et al. [15], has suggested that lung volume decreases significantly in the POSA group when moving from the lateral to the supine position, while there is no significant change in lung volume with position changing in the NPOSA group. Decreased lung volume can increase upper airway collapsibility via caudal tracheal displacement [28,29], which may be a trigger for upper airway collapse in the supine position in the POSA group [15]. However, these studies [15,23] were performed either in only severe OSA samples or by comparing both groups with unmatched AHI.

Therefore, whether POSA in comparison to NPOSA has its distinct pathophysiology characteristics still needs more research.

4.4 Limitations

This study has several limitations. First, the patients were awake during the CBCT examination, which may not accurately reflect upper airway morphology during sleep. However, taking CBCT images during sleep is quite challenging, therefore, upper airway imaging in the awake state has been widely used to study the underlying pathogenesis of OSA [30]. As the CBCT images were taken in the supine position for both groups in the present study, we assume that the comparison results are valid. However, sleep-induced changes in upper airway morphology may be different in both groups. Therefore, future research performed in the sleep state is needed to verify the current results. Second, the CBCT measurements were collected as part of a previous treatment study [16] and, hence, only taken in the supine position. Images in non-supine positions would show whether the current non-significant findings are also applicable in other sleeping positions. Future research, including scans in both positions, is therefore recommended. Moreover, as this study recruited patients from a prospective study [16], we did not perform an a priori power analysis to calculate the sample size. However, the effect sizes of the primary outcome variables indicates that the differences in the anatomical balance and the CSAmin-shape between both groups are not clinically relevant. Third, the present study used Cartwright's definition [17] to classify POSA, which is the most commonly used definition to date. However, compared to other definitions [31-34], Cartwright's definition is the most lenient one and can result in a higher prevalence of POSA [32,35]. Therefore, our study possibly overestimated POSA, which may explain the relatively high prevalence of POSA (72%) and the non-significant findings. However, we did also test our results with the stricter definition of the Amsterdam Positional OSA Classification (APOC) [32]. Although some patients who did not have sufficient sleep time in supine and/or non-supine positions were excluded from the classification by using the APOC definition (reducing the total sample size to n = 38), the prevalence of POSA was similar (APOC vs Cartwright: 71% vs 72%), and the comparison results of the primary outcome variables were similar to the present ones. Therefore, the criteria used in the current study did not lead to biased results. POSA tends to be associated with mild and moderate OSA as opposed to severe OSA [31], and the majority of this study population (62%) was diagnosed with mild to moderate OSA, which may explain the high prevalence of POSA in our population.

5. Conclusions

Adults with POSA and adults with NPOSA have similar anatomical balance and shape of their upper airway in the supine position.

Funding
Xiaoxin Shi received a scholarship from the China Scholarship Council. This work was supported by the National Health and Medical Research Council (NHMRC) of Australia (Project grant GNT1024351).

Competing interests
Xiaoxin Shi declares that she has no conflicts of interest. **Kate Sutherland** has received in kind support from SomnoMed Australia in the form of donation of oral appliances for investigator-initiated research. **Frank Lobbezoo** is a member of the Academic Advisory Boards for GrindCare and Oral Function of Sunstar Suisse S.A. and receives research grants from Sunstar Suisse S.A., SomnoMed, Vivisol BV, Health Holland, and Airway Management. **Erwin Berkhout** declares that he has no conflicts of interest. **Jan de Lange** declares that he has no conflicts of interest. **Peter A. Cistulli** holds the ResMed Chair in Sleep Medicine at the University of Sydney, established through funding from ResMed. He is a consultant to ResMed, SomnoMed, and Signifier Medical Technologies and has receive equipment support for research. **M. Ali Darendeliler** declares that he has no conflicts of interest. **Oyku Dalci** declares that she has no conflicts of interest. **Ghizlane Aarab** is a member of the Academic Advisory Board for Oral Function of Sunstar Suisse S.A. and receives research grants from Sunstar Suisse S.A., SomnoMed, Vivisol BV, and Health Holland.

References

1. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF (2012) Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events: deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. Journal of clinical sleep medicine 8 (5):597-619
2. Oksenberg A, Arons E, Radwan H, Silverberg DS (1997) Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic and multiple sleep latency test data. Chest 112 (3):629-639
3. Teerapraipruk B, Chirakalwasan N, Simon R, Hirunwiwatkul P, Jaimchariyatam N, Desudchit T, Charakorn N, Wanlapakorn C (2012) Clinical and polysomnographic data of positional sleep apnea and its predictors. Sleep and Breathing 16 (4):1167-1172
4. Sabil A, Blanchard M, Trzepizur W, Goupil F, Meslier N, Paris A, Pigeanne T, Priou P, Le Vaillant M, Gagnadoux F (2020) Positional obstructive sleep apnea within a large multicenter French cohort: prevalence, characteristics, and treatment outcomes. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 16 (12):2037-2046. doi:10.5664/jcsm.8752
5. Joosten SA, O'Driscoll DM, Berger PJ, Hamilton GS (2014) Supine position related obstructive sleep apnea in adults: pathogenesis and treatment. Sleep medicine reviews 18 (1):7-17
6. Pevernagie DA, Stanson A, Sheedy 2nd P, Daniels BK, Shepard Jr JW (1995) Effects of body position on the upper airway of patients with obstructive sleep apnea. American journal of respiratory and critical care medicine 152 (1):179-185
7. Lee CH, Kim S-W, Han K, Shin J-M, Hong S-L, Lee J-E, Rhee C-S, Kim J-W (2011) Effect of uvulopalatopharyngoplasty on positional dependency in obstructive sleep apnea. Archives of Otolaryngology–Head & Neck Surgery 137 (7):675-679
8. Sutherland K, Takaya H, Qian J, Petocz P, Ng AT, Cistulli PA (2015) Oral appliance treatment response and polysomnographic phenotypes of obstructive sleep apnea. Journal of Clinical Sleep Medicine 11 (8):861-868
9. Lee RW, Sutherland K, Cistulli PA (2010) Craniofacial morphology in obstructive sleep apnea: a review. Clinical Pulmonary Medicine 17 (4):189-195
10. Tsuiki S, Isono S, Ishikawa T, Yamashiro Y, Tatsumi K, Nishino T (2008) Anatomical Balance of the Upper Airway and Obstructive Sleep Apnea. Anesthesiology 108 (6):1009-1015. doi:10.1097/ALN.0b013e318173f103
11. Sutherland K, Almeida FR, de Chazal P, Cistulli PA (2018) Prediction in obstructive sleep apnoea: diagnosis, comorbidity risk, and treatment outcomes. Expert Review of Respiratory Medicine 12 (4):293-307
12. ISONO S (2012) Obesity and obstructive sleep apnoea: Mechanisms for increased collapsibility of the passive pharyngeal airway. Respirology 17 (1):32-42. doi:https://doi.org/10.1111/j.1440-1843.2011.02093.x
13. Jiao X, Zou J, Liu S, Guan J, Yi H, Yin S (2017) A retrospective study: does upper airway morphology differ between non-positional and positional obstructive sleep apnea? PeerJ 5:e3918
14. Saigusa H, Suzuki M, Higurashi N, Kodera K (2009) Three-dimensional morphological analyses of positional dependence in patients with obstructive sleep apnea syndrome. Anesthesiology: The Journal of the American Society of Anesthesiologists 110 (4):885-890
15. Joosten SA, Sands SA, Edwards BA, Hamza K, Turton A, Lau KK, Crossett M, Berger PJ, Hamilton GS (2015) Evaluation of the role of lung volume and airway size and shape in supine-predominant obstructive sleep apnoea patients. Respirology 20 (5):819-827
16. Sutherland K, Chan AS, Ngiam J, Dalci O, Darendeliler MA, Cistulli PA (2018) Awake multimodal phenotyping for prediction of oral appliance treatment outcome. Journal of Clinical Sleep Medicine 14 (11):1879-1887
17. Cartwright RD (1984) Effect of sleep position on sleep apnea severity. Sleep 7 (2):110-114
18. Walter SD, Eliasziw M, Donner A (1998) Sample size and optimal designs for reliability studies. Statistics in medicine 17 (1):101-110. doi:10.1002/(sici)1097-0258(19980115)17:1<101::aid-sim727>3.0.co;2-e
19. Chen H, Aarab G, Parsa A, de Lange J, van der Stelt PF, Lobbezoo F (2016) Reliability of three-dimensional measurements of the upper airway on cone beam computed tomography images. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 122 (1):104-110
20. Koo TK, Li MY (2016) A guideline of selecting and reporting intraclass correlation coefficients for reliability research. Journal of chiropractic medicine 15 (2):155-163
21. Cohen J (1988) Statistical Power Analysis for the Behavioral Sciences (2nd ed.). Routledge. https:// doi.org/ 10. 4324/ 97802 03771 587
22. Ogawa T, Enciso R, Shintaku WH, Clark GT (2007) Evaluation of cross-section airway configuration of obstructive sleep apnea. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology

103 (1):102-108
23. Joosten SA, Edwards BA, Wellman A, Turton A, Skuza EM, Berger PJ, Hamilton GS (2015) The effect of body position on physiological factors that contribute to obstructive sleep apnea. Sleep 38 (9):1469-1478
24. McSharry D, O'Connor C, McNicholas T, Langran S, O'Sullivan M, Lowery M, McNicholas WT (2012) Genioglossus fatigue in obstructive sleep apnea. Respiratory physiology & neurobiology 183 (2):59-66. doi:10.1016/j.resp.2012.05.024
25. Kim AM, Keenan BT, Jackson N, Chan EL, Staley B, Poptani H, Torigian DA, Pack AI, Schwab RJ (2014) Tongue fat and its relationship to obstructive sleep apnea. Sleep 37 (10):1639-1648. doi:10.5665/sleep.4072
26. Saboisky JP, Butler JE, Fogel RB, Taylor JL, Trinder JA, White DP, Gandevia SC (2006) Tonic and Phasic Respiratory Drives to Human Genioglossus Motoneurons During Breathing. Journal of Neurophysiology 95 (4):2213-2221. doi:10.1152/jn.00940.2005
27. Saboisky JP, Butler JE, Gandevia SC, Eckert DJ (2012) Functional role of neural injury in obstructive sleep apnea. Frontiers in neurology 3:95. doi:10.3389/fneur.2012.00095
28. Stanchina ML, Malhotra A, Fogel RB, Trinder J, Edwards JK, Schory K, White DP (2003) The influence of lung volume on pharyngeal mechanics, collapsibility, and genioglossus muscle activation during sleep. Sleep 26 (7):851-856. doi:10.1093/sleep/26.7.851
29. Tong J, Jugé L, Burke PG, Knapman F, Eckert DJ, Bilston LE, Amatoury J (2019) Respiratory-related displacement of the trachea in obstructive sleep apnea. Journal of applied physiology (Bethesda, Md : 1985) 127 (5):1307-1316. doi:10.1152/japplphysiol.00660.2018
30. Chen H, Aarab G, de Ruiter MH, de Lange J, Lobbezoo F, van der Stelt PF (2016) Three-dimensional imaging of the upper airway anatomy in obstructive sleep apnea: a systematic review. Sleep medicine 21:19-27
31. Mador MJ, Kufel TJ, Magalang UJ, Rajesh S, Watwe V, Grant BJ (2005) Prevalence of positional sleep apnea in patients undergoing polysomnography. Chest 128 (4):2130-2137
32. Frank M, Ravesloot M, Van Maanen J, Verhagen E, De Lange J, De Vries N (2015) Positional OSA part 1: towards a clinical classification system for position-dependent obstructive sleep apnoea. Sleep and breathing 19:473-480
33. Marklund M, Persson M, Franklin KA (1998) Treatment success with a mandibular advancement device is related to supine-dependent sleep apnea. Chest 114 (6):1630-1635
34. Bignold JJ, Mercer JD, Antic NA, McEvoy RD, Catcheside PG (2011) Accurate position monitoring and improved supine-dependent obstructive sleep apnea with a new position recording and supine avoidance device. Journal of clinical sleep medicine 7(4):376–383. https:// doi. org/ 10. 5664/ JCSM. 1194
35. Levendowski DJ, Oksenberg A, Vicini C, Penzel T, Levi M, Westbrook PR (2018) A systematic comparison of factors that could impact treatment recommendations for patients with Positional Obstructive Sleep Apnea (POSA). Sleep Medicine 50:145-151

Chapter 3

Comparison of the upper airway morphology between Dutch and Chinese adults with obstructive sleep apnea

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Published as: Shi, X., Chen, H., Lobbezoo, F., de Lange, J., van der Stelt, P., Berkhout, E., Guo, J., Ge, S., Li, G., Li, Y., & Aarab, G. (2023). Comparison of the upper airway morphology between Dutch and Chinese adults with obstructive sleep apnea. Sleep & breathing = Schlaf & Atmung, 10.1007/s11325-023-02834-z. Advance online publication. https://doi.org/10.1007/s11325-023-02834-z

Abstract

Purpose

The pathogenesis of obstructive sleep apnea (OSA) is complex and may vary between different races. It has been suggested that the anatomical balance between skeletal tissues and soft tissues around the upper airway is a key pathophysiologic factor of OSA. Therefore, the aim of this study was to compare the anatomical balance of the upper airway between Dutch and Chinese patients with OSA based on cone beam computed tomography (CBCT) images.

Methods

This was a cross-sectional study performed in two centers and included Dutch and Chinese adults with OSA. CBCT scans in the supine position were obtained for both Dutch and Chinese OSA groups. The primary outcome variable was the anatomical balance of the upper airway, defined as the ratio of the tongue area and the maxillomandibular enclosure area.

Results

A total of 28 Dutch adults (mean age ± SD of 46.6 ± 14.1 years, body mass index [BMI] of 26.8 ± 3.5 kg/m^2, and apnea-hypopnea index [AHI] of 15.7 ± 7.1 events/h) and 24 Chinese adults (age 41.0 ± 12.4 years, BMI 26.5 ± 3.3 kg/m^2, and AHI 16.5 ± 7.8 events/h). There were no significant differences in AHI, age, BMI, and sex between the two groups (P = 0.14-0.76). The Dutch group had a significantly larger tongue area and tongue length compared to the Chinese group (P = 0.01 and P < 0.01). On the other hand, the Chinese group had a smaller maxilla length compared to the Dutch group (P < 0.01). However, the anatomical balance of the upper airway of both groups was not significantly different (P = 0.16).

Conclusion

Within the limitations of this study, no significant difference was found in the anatomical balance of the upper airway between Dutch and Chinese patients with mild to moderate OSA.

Keywords

Obstructive sleep apnea, Races, Upper airway morphology, Anatomical balance, Cone beam computed tomography

1. Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent complete and/or partial obstructions of the upper airway, often resulting in arousals from sleep and oxygen desaturations [1]. Excessive daytime sleepiness, lack of concentration, and fatigue are examples of frequent complaints of patients with OSA [2]. The pathogenesis of OSA involves a complex interaction of anatomical and non-anatomical factors, among which a narrowed upper airway plays a key role [3]. It has been suggested that the pathogenesis of OSA may vary between different races; however, the exact difference is still unclear [4,5].

Both restricted skeletal structures and enlarged soft tissues can lead to a narrowed upper airway [6,7]. Specifically, the anatomical balance of the upper airway, defined as the ratio of the tongue size and the maxillomandibular enclosure size, is a key determinant of upper airway morphology [8]. Studies have indicated that, when the OSA severity is similar, Caucasian adults with OSA are more overweight (e.g., greater body mass index (BMI) and neck circumference), whereas Asian adults with OSA show more severe skeletal restrictions (e.g., a smaller maxilla and mandible, and retrognathia) [9-12]. These findings indicate that the anatomical balance of the upper airway may be similar between the two races.

Only a few studies have performed a direct inter-race comparison of the anatomical balance. However, their results are inclusive. A study of Schorr et al. [11] has suggested that Caucasians with OSA had a greater anatomical imbalance as compared with the Japanese-Brazilians with OSA. On the other hand, the study of Lee et al. [10] has suggested a similar anatomical balance between Caucasian and Chinese patients with OSA. The different results could be due to different races being compared. Besides, their results may be biased by using an inaccurate definition of the anatomical balance. Since the anatomical balance is involved in the pathogenesis of OSA [8,13], and is also an important predictor of treatment outcome of OSA [14], a better understanding of the role of anatomical balance between different races is necessary. This may help to improve OSA recognition and result in a more targeted therapy for specific racial groups.

According to the current evidence, we hypothesized that the anatomical balance of the upper airway (i.e., the ratio of the tongue area and the maxillomandibular enclosure area) is similar between Dutch and Chinese patients with OSA. To investigate upper airway morphology, cone beam computed tomography (CBCT) has been suggested to be a reliable technique [15,16] with lower radiation dose and costs compared to traditional CT [17,18]. Therefore, the aim of this study was

to compare the anatomical balance of the upper airway between Dutch and Chinese patients based on CBCT images.

2. Material and methods

2.1 Overview

This was a cross-sectional study in which participants were recruited from both the Amsterdam University Medical Center (AUMC) in the Netherlands and the Qilu Hospital of Shandong University in China. Dutch participants were recruited from a randomized controlled trial (RCT) (ClinicalTrials.gov identifier: NCT02724865), which was designed to compare the treatment effects of two different types of mandibular advancement device (MAD) in patients with mild and moderate OSA. Chinese participants were recruited prospectively for this study.

The protocol for recruiting the patients from the Netherlands was approved by the Medical Ethics Committee of the AUMC with reference number NL44085.018.13/ COSH. The protocol of recruiting patients from China was approved by the Medical Ethics Committee of the Dental School of Shandong University with reference number NO.GR201814.

Written informed consent was obtained from both Dutch and Chinese patients. The present study was registered at the ClinicalTrials.gov identifier NCT03463785.

2.2 Recruitment

Patients that fit the following inclusion/exclusion criteria were recruited in both the Netherlands and China. The inclusion criteria were as follows: (1) age ≥ 18 years; (2) able to speak, read, and write either Dutch or Chinese; (3) able to follow up; (4) diagnosed with symptomatic mild or moderate OSA (5 ≤ apnea-hypopnea index (AHI) < 30); and (5) expected to be able to maintain their current lifestyle (sports, medicine, diet, etc.).

The exclusion criteria were as follows: (1) medication use related to sleeping disorders; (2) evidence of respiratory and/or sleep disorders other than OSA (e.g., central sleep apnea syndrome); (3) systemic disorders (based on medical history and examination, e.g., rheumatoid arthritis); (4) medical history of known daytime fatigue or severe sleep disturbance (e.g., insomnia, PLMS, narcolepsy); (5) known medical history of mental retardation, memory impairment, or psychiatric disorders; (6) reversible morphological upper airway abnormalities (viz., indication for upper airway surgery); (7) syndromes with craniofacial abnormalities (e.g.,

Pierre Robin sequence and Down syndrome); and (8) inability to provide informed consent. As the Dutch OSA group was recruited from an RCT study, there were two extra exclusion criteria for this group: (1) untreated periodontal problems/ toothache/lack of retention possibilities for an MAD, and (2) concomitant use of other modalities to treat OSA.

2.3 Polysomnography (PSG)

All Dutch participants included in this study underwent an overnight PSG recording (Embla A10, Broomfield, CO, USA) at one of the four participating sleep centers (Onze Lieve Vrouwe Gasthuis Ziekenhuis (OLVG), Nederlands Slaap Instituut, Medisch Centrum Jan van Goyen, and Amsterdam Medical Center) in Amsterdam for the diagnosis of OSA. All Chinese participants included in this study underwent an overnight PSG recording (Alice 6, Phillips Respironics, USA) at the Qilu Hospital in Jinan for the diagnosis of OSA.

PSG included the following variables: electroencephalogram, electrooculogram, leg and chin electromyograms, electrocardiogram, pulse oximetry, body position, neck microphone, nasal cannula pressure transducer, and inductive plethysmography by means of thoracic and abdominal bands. The PSG recordings were manually scored in a standard manner for both Dutch and Chinese OSA groups [19]. Apnea was defined as a cessation of airflow of ≥ 90% for at least 10 s. Hypopnea was defined as a decrease in airflow of more than 30% for at least 10 s, accompanied by either ≥ 3% oxygen desaturation or an arousal [19]. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep.

2.4 Cone beam computed tomography (CBCT)

The CBCT datasets of Dutch and Chinese patients were obtained using identical NewTom 5G CBCT systems (QR systems, Verona, Italy), according to a standard imaging protocol [15]. In the Netherlands, CBCT scans of the patients were made at the Department of Oral Radiology at the Academic Centre for Dentistry Amsterdam (ACTA). In China, CBCT scans of the patients were made at the Department of Oral Radiology, School of Dentistry, Shandong University.

During the imaging procedure, automatic exposure control was applied, and the patients were positioned in a supine position with the Frankfort horizontal (FH) plane being perpendicular to the floor [15]. They were instructed to maintain light contact between the molars in natural occlusion, to keep quiet breathing, and to avoid swallowing and other movements during the scanning period. The exposure settings were 110 kV, 4 mA, 0.3 mm voxel size, 3.6 s exposure time (pulsed radiation), and 18-36 s scanning time, depending on the size of the patient [15]. To get a

standardized head position of each CBCT image, re-orientation was performed by adjusting the palatal plane (the plane crossing anterior nasal spine (ANS)-posterior nasal spine (PNS)) being parallel to the global horizontal plane in the sagittal view, and perpendicular to the global horizontal plane in the axial view [20]. For further analysis, the images were saved as digital imaging and communications in medicine (DICOM) files. All images were presented to the observers in a room with dimmed light.

2.5 Primary outcome variable: anatomical balance of the upper airway

Anatomical balance of the upper airway was calculated using the ratio of the tongue area and the maxillomandibular enclosure area, which were measured on the mid-sagittal plane of CBCT imaging using 3Diagnosys® software (v5.3.1, 3diemme, Cantu, Italy). The tongue area (mm^2) was determined by the area enclosed by the point hyoid, menton, the contour of the frontal teeth and the tongue, and the base of the epiglottis (**Fig. 1A**). The maxillomandibular enclosure area (mm^2) was determined by the area enclosed by the point hyoid, menton, the contour of the front teeth, the hard palate, the posterior nasal spine, and the anterior boundary of the second and third cervical vertebra (**Fig. 1B**).

The values of the anatomical balance range between 0 and 1, and a larger value of the anatomical balance means the tongue occupied a larger section of the maxillomandibular enclosure area compared to a smaller value.

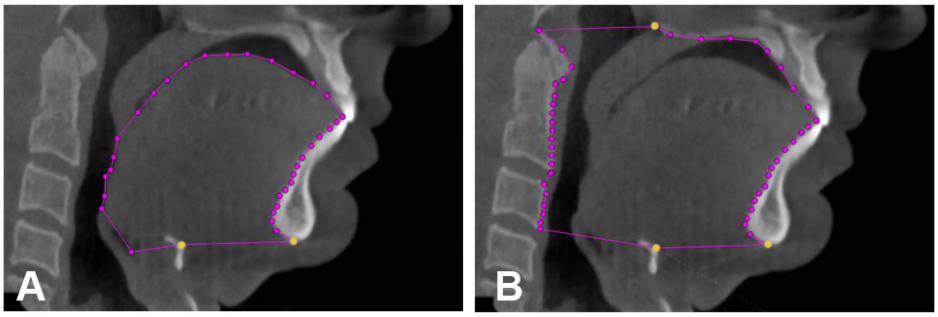

Fig. 1 The measurements of the tongue area and the maxillomandibular enclosure area on the mid-sagittal plane of a CBCT image (an example from the Dutch group). **A.** The tongue area. **B.** The maxillomandibular enclosure area

2.6 Secondary outcome variables

Secondary outcome variables of the upper airway morphology, including the structures of maxillomandibular enclosure, tongue, soft palate, the maxilla, and the

mandible, were measured using 3Diagnosys® software (v5.3.1, 3diemme, Cantu, Italy). The definitions and illustrations of the secondary variables are shown in **Table 1** and **Fig. 2**.

Table 1 Definitions of the primary and secondary outcome variables of the upper airway morphology

Structures	Variables	Definitions
Primary outcome variable		
Anatomical balance	Anatomical balance	Ratio of the tongue area and the maxillomandibular enclosure area
Secondary outcome variables		
Maxillomandibular enclosure	Maxillomandibular enclosure area	Area enclosed by the point hyoid, menton, the contour of the front teeth, the hard palate, the posterior nasal spine, and the anterior boundary of the second and third cervical vertebra
Tongue	Tongue area	Area enclosed by the point hyoid, menton, the contour of the frontal teeth and the tongue, and the base of the epiglottis
	Tongue length	Distance between the tip of tongue and the base of epiglottis
Soft palate	Soft palate length	Distance between the posterior nasal spine (PNS) and tip of soft palate
	Soft palate thickness	Maximum thickness of soft palate measured on the line perpendicular to the line of PNS - tip of soft palate
Maxilla	Maxilla length	Distance between the anterior nasal spine (ANS) and PNS
Mandible	Mandibular length	Distance between the gonion (Go) and menton (Me)

2.7 Statistical analysis

The Shapiro-Wilk test was used to test whether the data were normally distributed. The Mann-Whitney *U* test (for non-normally distributed variables), the independent *t*-test (for normally distributed variables), and the chi-squared test (for categorical variables) were used to compare the demographic characteristics, and the primary and secondary outcome variables of the upper airway morphology between the Dutch and Chinese OSA groups. Bonferroni-Holm correction was applied to the comparisons of secondary outcome variables of the upper airway [21]. Statistical analyses were performed using IBM® SPSS® Statistics for Macintosh, Version 26 (IBM Corp., Armonk, N.Y., USA).

The effect size was calculated for the anatomical balance by the software G*power (version 3.1.9, Franz Faul, Universität Kiel, Germany).

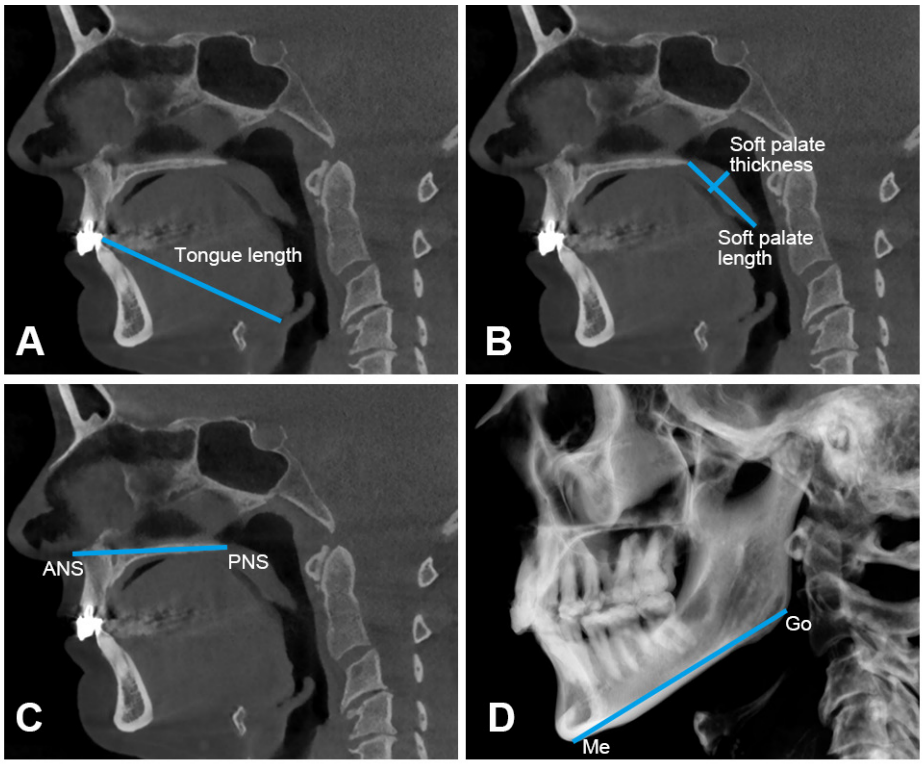

Fig. 2 Illustration of the secondary outcome variables of the upper airway morphology (an example from the Dutch group). **A.** Tongue length. **B.** Soft palate length and soft palate thickness. **C.** Maxilla length: distance between ANS (anterior nasal spine) and PNS (posterior nasal spine). **D.** Mandibular length: distance between Go (gonion) and Me (menton)

3. Results

3.1 Baseline characteristics

There were 28 Dutch patients and 24 Chinese patients fulfilling the requirements of inclusion and exclusion criteria included in the study. The demographic characteristics of the Dutch and Chinese patients are shown in **Table 2**. There were no significant differences in age, sex, body mass index (BMI), and apnea-hypopnea index (AHI) between the Dutch and Chinese patients (P = 0.14-0.76).

3.2 Comparisons of the upper airway morphology

The variables of the upper airway morphology of the Dutch and Chinese patients are shown in **Table 3**. The Dutch group had a significantly larger tongue area (T = 2.60, P = 0.01) and a larger tongue length (Z = -3.14, P < 0.01) compared to the Chinese group. On the other hand, the Chinese group had a smaller maxilla length

compared to the Dutch group (T = 7.34, P < 0.01). However, the anatomical balance of the upper airway of both groups was not significantly different (T = 1.43, P = 0.16). The effect size d, which is defined as a standardized difference in the means of the anatomical balance of the upper airway between both groups, was 0.4, which can be regarded as between small and medium (the effect size d of 0.20 is small, one of 0.5 is medium, and one of 0.8 is large [22]).

Table 2 Baseline demographic characteristics of the Dutch and Chinese OSA patients included in the study

	Dutch patients (n = 28)	Chinese patients (n = 24)	T or X^2	P
Age (year)	46.6 ± 14.1	41.0 ± 12.4	1.50 (T)	0.14
Sex (female vs male)	8 vs 20	4 vs 20	1.03 (X^2)	0.31
BMI (kg/m^2)	26.8 ± 3.5	26.5 ± 3.3	0.31 (T)	0.76
AHI (events/hour)	15.7 ± 7.1	16.5 ± 7.8	-0.36 (T)	0.72

Data are shown as mean ± standard deviation (SD); *T,* independent *t*-test; *X,*^{2} chi-squared test; *BMI,* body mass index; *AHI,* apnea-hypopnea index

Table 3 The variables of the upper airway morphology of the Dutch and Chinese patients

Variables	Dutch patients (n = 28)	Chinese patients (n = 24)	T/Z	P
Primary outcome variable				
Anatomical balance	0.70 ± 0.1	0.68 ± 0.0	1.43 (T)	0.16
Secondary outcome variables				
Maxillomandibular enclosure size				
Maxillomandibular enclosure area (cm^2)	4.9 ± 0.6	4.7 ± 0.4	1.81 (T)	0.08
Tongue				
Tongue area (cm^2)	3.4 ± 0.4	3.2 ± 0.3	2.60 (T)	0.01*
Tongue length (cm)	7.6 (7.0, 8.1)	6.9 (6.6, 7.4)	-3.14 (Z)	<0.01*
Soft palate				
Soft palate length (cm)	4.1 (3.8, 4.4)	4.0 (3.7, 4.1)	-1.65 (Z)	0.10
Soft palate thickness (cm)	1.0 ± 0.2	0.9 ± 0.2	2.17 (T)	0.04
Maxilla				
Maxilla length (cm)	5.6 ± 0.4	4.9 ± 0.3	7.34 (T)	<0.01*
Mandible				
Mandibular length (cm)	7.3 ± 0.6	7.1 ± 0.5	1.55 (T)	0.13

Normally distributed data are shown as mean ± standard deviation (SD); Non-normally distributed data are shown as median (25th percentile, 75th percentile); *T,* independent *t*-test; *Z,* Mann-Whitney *U* test; *Significant difference with Bonferroni-Holm correction

4. Discussion

The aim of the present study was to compare the anatomical balance of the upper airway between Dutch and Chinese patients with OSA. The results indicated that the Dutch group had a significantly larger tongue area and a larger tongue length compared to the Chinese group, while the Chinese group had a smaller maxilla length compared to the Dutch group. However, the anatomical balance of the upper airway of both groups was not significantly different.

4.1 Comparisons of the upper airway morphology

For the primary outcome variable, we did not find a significant difference in the anatomical balance of the upper airway between Dutch and Chinese patients with OSA. Further, the observed effect size d for the difference in the anatomical balance of the upper airway was 0.4, which is between small and medium. With this effect size, the difference in the anatomical balance between both groups may be not clinically relevant either [23,24]. In contrast to our results, a study of Schorr et al. [11] has suggested that Caucasians with OSA have a larger anatomical imbalance compared with the Japanese-Brazilians with OSA. However, for calculating the anatomical balance, they used the volume of the bony tissue rather than the volume of the bony enclosure as the denominator, which may cause bias and explain the different results as compared to our results. A study of Lee et al. [10] has suggested a similar anatomical balance between Caucasian and Chinese OSA groups, which is similar to our results. However, they used a simplified definition of the anatomical balance, defined as ratios of BMI to mandibular and maxillary bony dimensions, which may be less accurate. The definition used in the present study has been used widely in the literature to investigate the role of the anatomical balance of the upper airway in the pathogenesis and treatment of OSA [13,14,25]. Thus, by using a more generalized and accurate definition, the present study confirms that the anatomical balance of the upper airway is similar in Dutch and Chinese OSA groups.

For the secondary outcome variables, the Dutch group had a significantly larger tongue size and larger tongue length compared to the Chinese group. These results are similar to those of previous studies [9-12], which indicates that when the OSA severity is similar, Caucasian patients are more overweight, while Asian patients tend to have a smaller maxilla and mandible.

Previous studies have suggested that the craniofacial skeletal difference between Asians and Caucasians, such as restricted bony structures in Asians, is an important reason for a greater tendency of OSA development in Asians [9,26]. However, both bony structures and soft tissues can influence the upper airway morphology. By

taking into account both factors, the present study indicates that the anatomical imbalance may be similar for both groups. However, in addition to the anatomical factor, several non-anatomical factors are also crucial determinants for upper airway collapse, such as impaired upper airway dilator muscle activity, ventilatory control stability (i.e., high loop gain), and low arousal threshold [27]. The study of Lee et al. [28] has suggested that a low arousal threshold is a less common mechanism in the pathogenesis of the Chinese OSA group compared to the Caucasian OSA group. Further, the study of O'Driscoll et al. [29] has suggested that the loop gain is significantly higher in the Caucasian group than in the Chinese group. However, both studies included moderate-to-severe OSA patients, which may represent a different study sample as compared to our study. To the best of our knowledge, the difference in the non-anatomical factors between both races in patients with mild-to-moderate OSA is not clear yet. Understanding the individual pathogenesis can help in a personalized treatment approach in OSA [27]. Therefore, future research is needed to investigate the roles of anatomical and non-anatomical factors in the pathogenesis of OSA.

4.2 Demographic characteristics

Lee et al. [10] have suggested that the referral approach for the clinical assessment of OSA may be influenced by the differences in socioeconomic status, cultural, and environmental factors between the Caucasian and Chinese groups. This is consistent with the phenomenon that we discovered during the recruitment process. There were more patients with severe OSA referred to the sleep laboratory in China than in the Netherlands. To minimize the selection bias, we only recruited patients with mild to moderate OSA in both groups. Besides, both groups were similar in BMI, age, and sex. Therefore, the comparisons of the upper airway morphology between both groups were not biased by these factors.

4.3 Clinical relevance

Based on the non-significant results of the present study, it is possible that the anatomical balance of the upper airway plays a similar role in the pathogenesis of OSA in both races. Therefore, it may be speculated that treatment, which mainly targets the anatomical factors, might result in similar treatment results in both groups. Further studies will be performed in our lab to evaluate the treatment effects of the therapy in both races.

4.4 Limitations

There are several limitations in the present study. First, this study is a multi-center study recruiting Dutch and Chinese patients separately from two sites, which might cause selection bias. However, one of the investigators (H.C.) visited

both clinics to make sure that the protocol was implemented in the same way in both the Netherlands and China. Second, in our study, we defined the Dutch and Chinese races of the patients based on their family trees and names, which might cause selection bias. However, the definition of race in the medical literature is not always clear [30]. Contrary to other studies, our definition of race relied on family history rather than on the assumptions of the investigators, which could be a better approach in epidemiological studies [10]. Third, there are 56 ethnic groups in China, and previous studies concluded that the genetic structure is different among different ethnic groups in China [31,32]. As the craniofacial structure of patients is influenced by genetic factors [33], it is possible that there could be a difference in the craniofacial structure from different ethnic groups in China. In this study, we therefore recruited the Chinese patients only from the Han ethnic group. We excluded the effect of the living environment by recruiting only Dutch patients living in the Netherlands and Chinese patients living in Shandong, China. The measurements of the tongue area and the maxillomandibular enclosure area were based on the mid-sagittal plane of the CBCT imaging, and not on 3D volume measurements. The volume measurements in CBCT images were limited by the difficulty in discriminating between the different soft-tissue structures (due to similar Hounsfield units).

5. Conclusion

Within the limitations of this study, we conclude that there is no significant difference in the anatomical balance of the upper airway between Dutch and Chinese patients with mild to moderate OSA.

Acknowledgement
The authors gratefully acknowledge Dr. Naichuan Su, department of oral public health, Academic Centre for Dentistry Amsterdam (ACTA), for his assistance with the statistical analyses of this study.

Funding
This work was supported by the Royal Netherlands Academy of Arts and Sciences (KNAW; 530-5CDP12), and the Young Clinical Research Fund of the Chinese Stomatological Association (CSA-O2022-08). Xiaoxin Shi has received a scholarship from the China Scholarship Council.

Competing interests
Xiaoxin Shi declares that she has no conflicts of interest. **Hui Chen** declares that she

has no conflicts of interest. **Frank Lobbezoo** is a member of the Academic Advisory Boards for GrindCare and Oral Function of Sunstar Suisse S.A. and receives research grants from Sunstar Suisse S.A., SomnoMed, Vivisol BV, Health Holland, and Airway Management. **Jan de Lange** declares that he has no conflicts of interest. **Paul van der Stelt** declares that he has no conflicts of interest. **Erwin Berkhout** declares that he has no conflicts of interest. **Jing Guo** declares that she has no conflicts of interest. **Shaohua Ge** declares that she has no conflicts of interest. **Guoju Li** declares that she has no conflicts of interest. **Yanzhong Li** declares that he has no conflicts of interest. **Ghizlane Aarab** is a member of the Academic Advisory Board for Oral Function of Sunstar Suisse S.A. and receives research grants from Sunstar Suisse S.A., SomnoMed, Vivisol BV, and Health Holland.

References

1. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. (1999). Sleep 22 (5):667-689
2. Engleman H, Douglas N (2004) Sleep· 4: Sleepiness, cognitive function, and quality of life in obstructive sleep apnoea/hypopnoea syndrome. Thorax 59 (7):618-622
3. Carberry JC, Amatoury J, Eckert DJ (2018) Personalized management approach for OSA. Chest 153 (3):744-755
4. Sutherland K, Lee RW, Cistulli PA (2012) Obesity and craniofacial structure as risk factors for obstructive sleep apnoea: impact of ethnicity. Respirology 17 (2):213-222
5. Hnin K, Mukherjee S, Antic NA, Catcheside P, Chai-Coetzer CL, McEvoy D, Vakulin A (2018) The impact of ethnicity on the prevalence and severity of obstructive sleep apnea. Sleep medicine reviews 41:78-86
6. Schwab RJ, Pasirstein M, Pierson R, Mackley A, Hachadoorian R, Arens R, Maislin G, Pack AI (2003) Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. American journal of respiratory and critical care medicine 168 (5):522-530
7. Neelapu BC, Kharbanda OP, Sardana HK, Balachandran R, Sardana V, Kapoor P, Gupta A, Vasamsetti S (2017) Craniofacial and upper airway morphology in adult obstructive sleep apnea patients: a systematic review and meta-analysis of cephalometric studies. Sleep medicine reviews 31:79-90
8. Watanabe T, Isono S, Tanaka A, Tanzawa H, Nishino T (2002) Contribution of body habitus and craniofacial characteristics to segmental closing pressures of the passive pharynx in patients with sleep-disordered breathing. American journal of respiratory and critical care medicine 165 (2):260-265
9. Liu Y, Lowe AA, Zeng X, Fu M, Fleetham JA (2000) Cephalometric comparisons between Chinese and Caucasian patients with obstructive sleep apnea. American Journal of Orthodontics & Dentofacial Orthopedics 117 (4):479-485
10. Lee RW, Vasudavan S, Hui DS, Prvan T, Petocz P, Darendeliler MA, Cistulli PA (2010) Differences in craniofacial structures and obesity in Caucasian and Chinese patients with obstructive sleep apnea. Sleep 33 (8):1075-1080
11. Schorr F, Kayamori F, Hirata RP, Danzi-Soares NJ, Gebrim EM, Moriya HT, Malhotra A, Lorenzi-Filho G, Genta PR (2016) Different craniofacial characteristics predict upper airway collapsibility in Japanese-Brazilian and white men. Chest 149 (3):737-746
12. Xu L, Keenan BT, Wiemken AS, Chi L, Staley B, Wang Z, Wang J, Benedikstdottir B, Juliusson S, Pack AI, Gislason T, Schwab RJ (2019) Differences in three-dimensional upper airway anatomy between Asian and European patients with obstructive sleep apnea. Sleep 43 (5). doi:10.1093/sleep/zsz273
13. Tsuiki S, Isono S, Ishikawa T, Yamashiro Y, Tatsumi K, Nishino T (2008) Anatomical Balance of the Upper Airway and Obstructive Sleep Apnea. Anesthesiology 108 (6):1009-1015. doi:10.1097/ALN.0b013e318173f103
14. Mostafiz W, Dalci O, Sutherland K, Malhotra A, Srinivasan V, Darendeliler MA, Cistulli PA (2011) Influence of oral and craniofacial dimensions on mandibular advancement splint treatment outcome in patients with obstructive sleep apnea. Chest 139 (6):1331-1339
15. Chen H, Aarab G, Parsa A, de Lange J, van der Stelt PF, Lobbezoo F (2016) Reliability of three-dimensional measurements of the upper airway on cone beam computed tomography images. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 122 (1):104-110
16. Chen H, Van Eijnatten M, Aarab G, Forouzanfar T, De Lange J, Van Der Stelt P, Lobbezoo F, Wolff J (2018) Accuracy of MDCT and CBCT in three-dimensional evaluation of the oropharynx morphology. European journal of orthodontics 40 (1):58-64
17. Palomo JM, Kau CH, Palomo LB, Hans MG (2006) Three-dimensional cone beam computerized tomography in dentistry. Dentistry today 25 (11):130
18. Suomalainen A, Kiljunen T, Kaser Y, Peltola J, Kortesniemi M (2009) Dosimetry and image quality of four dental cone beam computed tomography scanners compared with multislice computed tomography scanners. Dentomaxillofacial Radiology 38 (6):367-378
19. Berry RB BR, Gamaldo CE, Harding SM, Lloyd RM, Marcus CL, et al. (2016) The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications, Version 2.3. www.aasmnet.org. Darien Illinois: American Academy of Sleep Medicine.
20. Weissheimer A, Menezes LM, Sameshima GT, Enciso R, Pham J, Grauer D (2012) Imaging software accuracy for 3-dimensional analysis of the upper airway. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics 142 (6):801-813. doi:10.1016/j.ajodo.2012.07.015
21. Armstrong RA (2014) When to use the Bonferroni correction. Ophthalmic & physiological optics : the journal of the British College of Ophthalmic Opticians (Optometrists) 34 (5):502-508. doi:10.1111/opo.12131

22. Cohen J (2013) Statistical power analysis for the behavioral sciences. Academic press,
23. Armijo-Olivo S, Warren S, Fuentes J, Magee DJ (2011) Clinical relevance vs. statistical significance: Using neck outcomes in patients with temporomandibular disorders as an example. Manual therapy 16 (6):563-572
24. Davis SL, Johnson AH, Lynch T, Gray L, Pryor ER, Azuero A, Soistmann HC, Phillips SR, Rice M (2021) Inclusion of Effect Size Measures and Clinical Relevance in Research Papers. Nursing research 70 (3):222-230. doi:10.1097/nnr.0000000000000494
25. Chen H, Aarab G, Lobbezoo F, De Lange J, Van der Stelt P, Darendeliler MA, Cistulli PA, Sutherland K, Dalci O (2019) Differences in three-dimensional craniofacial anatomy between responders and non-responders to mandibular advancement splint treatment in obstructive sleep apnoea patients. European Journal of Orthodontics 41 (3):308-315. doi:10.1093/ejo/cjy085
26. Chen X, Wang R, Lutsey PL, Zee PC, Javaheri S, Alcántara C, Jackson CL, Szklo M, Punjabi N, Redline S, Williams MA (2016) Racial/ethnic differences in the associations between obesity measures and severity of sleep-disordered breathing: the Multi-Ethnic Study of Atherosclerosis. Sleep Medicine 26:46-53. doi:https://doi.org/10.1016/j.sleep.2015.06.003
27. Eckert DJ (2018) Phenotypic approaches to obstructive sleep apnoea–new pathways for targeted therapy. Sleep medicine reviews 37:45-59
28. Lee RW, Sutherland K, Sands SA, Edwards BA, Chan To, S.S. NG S, Hui DS, Cistulli PA (2017) Differences in respiratory arousal threshold in Caucasian and Chinese patients with obstructive sleep apnoea. Respirology 22 (5):1015-1021. doi:https://doi.org/10.1111/resp.13022
29. O'Driscoll DM, Landry SA, Pham J, Young A, Sands SA, Hamilton GS, Edwards BA (2019) The physiological phenotype of obstructive sleep apnea differs between Caucasian and Chinese patients. Sleep 42 (11). doi:10.1093/sleep/zsz186
30. Villaneuva AT, Buchanan PR, Yee BJ, Grunstein RR (2005) Ethnicity and obstructive sleep apnoea. Sleep medicine reviews 9 (6):419-436. doi:10.1016/j.smrv.2005.04.005
31. Kong T, Chen Y, Guo Y, Wei Y, Jin X, Xie T, Mu Y, Dong Q, Wen S, Zhou B, Zhang L, Shen C, Zhu B (2017) Autosomal InDel polymorphisms for population genetic structure and differentiation analysis of Chinese Kazak ethnic group. Oncotarget 8 (34):56651-56658. doi:10.18632/oncotarget.17838
32. Yang CH, Yin CY, Shen CM, Guo YX, Dong Q, Yan JW, Wang HD, Zhang YD, Meng HT, Jin R, Chen F, Zhu BF (2017) Genetic variation and forensic efficiency of autosomal insertion/deletion polymorphisms in Chinese Bai ethnic group: phylogenetic analysis to other populations. Oncotarget 8 (24):39582-39591. doi:10.18632/oncotarget.17137
33. Kaparianos A, Sampsonas F, Karkoulias K, Spiropoulos K (2006) Obstructive sleep apnoea syndrome and genes. The Netherlands journal of medicine 64 (8):280-289

Chapter 4

Effects of miniscrew-assisted orthodontic treatment with premolar extractions on upper airway dimensions in adult patients with Class II high-angle malocclusion

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Published as: Shi, X., Chen, H., Lobbezoo, F., Berkhout, E., de Lange, J., Guo, J., & Aarab, G. (2021). Effects of miniscrew-assisted orthodontic treatment with premolar extractions on upper airway dimensions in adult patients with Class II high-angle malocclusion. American journal of orthodontics and dentofacial orthopedics: official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics, 159(6), 724–732. https://doi.org/10.1016/j.ajodo.2020.02.016

Abstract

Introduction

The primary aim of this study was to investigate the change in upper airway dimensions and in mandibular position after miniscrew-assisted treatment with premolar extractions in adult patients with Class II high-angle malocclusion. The secondary aim was to determine the correlation between changes in upper airway dimensions and changes in mandibular position in these patients.

Methods

Eighteen adult patients with Class II high-angle malocclusion (mean ± standard deviation age = 21.2 ± 2.9 years) were selected retrospectively. All patients underwent 4 premolars extraction, and 2 miniscrews were implanted in the maxilla to intrude molar height. Cone beam computed tomography images were taken pretreatment and posttreatment for every patient. The primary outcome variable for the upper airway was the minimal cross-sectional area of the upper airway (CSA_{min}), and the primary outcome variables for the mandible were mandibular rotation (Mp-SN angle), mandibular horizontal position (SNB angle), and mandibular vertical position (ANS-Me distance).

Results

The CSA_{min} significantly increased by 47.2 mm^2 (t = -2.26, P = 0.04) after orthodontic treatment. The mandible significantly rotated counterclockwise by 0.9° (t = 2.20, P = 0.04) after treatment, which consisted of forward movement of 1.2° (t = -4.30, P = 0.00) and upward movement of 1.3 mm (Z = -1.98, P = 0.05). Furthermore, the change of the CSA_{min} showed a significant correlation with the change of the ANS-Me (P = 0.01).

Conclusion

By using miniscrews to intrude maxillary molars, orthodontic premolar extraction treatment results in mandibular counterclockwise rotation, and upper airway dimensions increase in Class II high-angle young adult patients. The increase of the upper airway dimensions significantly correlates to the upward movement of the mandible.

Keywords

Premolar extraction, Miniscrew, Temporary skeletal anchorage device, Upper airway

1. Introduction

Class II high-angle malocclusion combines Class II Division 1 malocclusion and mandibular vertical excess [1], which is one of the most complex malocclusions in the field of orthodontics [2]. For dental malocclusion, orthodontic premolar extraction treatment is typically used to provide space to align crowded teeth, correct anteroposterior interarch discrepancies, and retract incisors [3]. However, traditional orthodontic treatment has only a small effect on mandibular vertical excess [4]. Orthognathic surgery can correct the mandibular position directly, but many patients do not accept this type of treatment [5]. An alternative treatment, as reported in a few studies, is to use skeletal anchorage (miniplates, miniscrews) to intrude molars, which leads to a significant counterclockwise rotation of the mandible and shortening of the mandibular vertical excess in patients with an open bite [6-9]. However, no previous studies were performed to study the effects of this treatment in patients with Class II high-angle malocclusion.

Patients with Class II high-angle malocclusion may tend to have a smaller upper airway [10,11] and a higher risk for obstructive sleep apnea (OSA) [12,13]. OSA is characterized by recurrent obstruction of the upper airway, often resulting in oxygen desaturations and arousals from sleep [14]. OSA is a common sleep-related disorder, affecting a mean of 22% (range, 9-37%) men and 17% (range, 4-50%) women [15]. Besides suffering from the common complaints such as snoring and excessive daytime sleepiness, severe OSA patients also develop cardiovascular problems, such as myocardial infarction and stroke [16]. As a constricted airway is one of the key factors to the pathogenesis of OSA [17], it is of importance to understand the effect of orthodontic treatment on upper airway dimensions of patients with Class II high-angle malocclusion.

Many studies [3,5,18-21] have discussed the effects of orthodontic teeth extraction treatment on upper airway dimensions in adult patients. However, the results were not consistent. One study found the upper airway increased after extraction using lateral cephalograms [22], whereas other studies found the upper airway narrowed after treatment based on lateral cephalograms [3,20] or multislice computed tomography images [21]. Besides, some studies reported that the upper airway remained unchanged after extraction based on cone beam computed tomography (CBCT) images [5,19] and lateral cephalograms [18]. These conflicting results might be related to different malocclusion types, treatment strategies, imaging techniques (2-dimensional vs 3-dimensional imaging techniques), and upper airway variables. Besides, the mandibular position change during treatment was not taken into consideration in previous studies. Thus, the effects of mandibular

position change on upper airway dimensions in adult patients with Class II high-angle malocclusion have not been determined yet.

As mandibular position is associated with upper airway dimensions via the lingual musculature (e.g., genioglossus muscle), we hypothesized that the counterclockwise rotation of the mandible as a result of an orthodontic treatment with the assistance of skeletal anchorage and premolar extractions would result in an increase in the upper airway dimensions. Therefore, the aims of this study were to determine in adult patients with Class II high-angle malocclusion: (1) the effects of miniscrew-assisted orthodontic extraction treatment on mandibular position and on upper airway dimensions; and (2) the correlation between the changes of mandibular position and the changes of upper airway dimensions.

2. Materials and Methods

This retrospective study was approved by the Ethics Committee of the Stomatology Hospital of Shandong University, Jinan, Shandong, China (No. R20180706). Participants were selected from among all patients treated from January 2015 to July 2017 at the orthodontic clinic of the Stomatology Hospital of Shandong University.

The inclusion criteria were (1) adult patients (age ≥ 18 years old); (2) Class II malocclusion (ANB angle ≥ 4°) and high-angle pattern (Mp-SN angle ≥ 37°) [5]; (3) extraction of the maxillary first premolars and mandibular second premolars; (4) 2 miniscrews implanted bilaterally in the maxilla; and (5) available CBCT images before treatment and after treatment. The exclusion criteria were (1) temporomandibular joint disorders; (2) congenital absence of permanent teeth; (3) history of upper airway surgery; (4) previous orthodontic treatment and/or orthognathic surgery; (5) self-reported snoring and/or sleep apnea; and (6) impairment in the lip and/or palate function, such as a cleft lip and/or palate.

After extracting the maxillary first premolars and mandibular second premolars, all patients underwent a pre-adjusted edgewise appliance of 0.022-inch slot McLaughlin, Bennett, Trevisi brackets (Tomy International, Tokyo, Japan). Two miniscrews of 8 mm length (Vector TAS, Ormco, Orange, Calif) were implanted bilaterally in the maxilla between the second premolars and the first molars around the apical region through the buccal mucosa after local anesthesia by the same orthodontist. Four weeks after the miniscrew placement, orthodontic intrusion load, estimated as 150 *g* of force, was applied using an elastic chain. Moderate

anchorage reinforcement was used in the maxilla to retract the maxillary anterior teeth, while minimal anchorage strategy was used in the mandible [23]. The treatment goal was Class I canine and/or molar relationship, and the treatment time for each patient was approximately 2 and a half years.

Galileos CBCT scans (Sirona Dental Systems, Bensheim, Germany) were taken before and after treatment in all patients. During the scan, patients stood in the CBCT machine with a natural upright head position and maximum intercuspation. They were instructed to breath quietly through nose and to avoid swallowing and other movements. The fixed field of view size was 15 cm ×15 cm. All CBCT images were taken by the same operator. The images were saved in Digital Imaging and Communications in Medicine format for further analysis.

To measure the mandibular position, the maxillary position, incisors position, and the hyoid position, 15 landmarks were identified according to the guidelines of American Board of Orthodontics, yielding 6 linear and 5 angular measurements (**Table 1; Fig. 1**). All measurements were done before and after treatment based on CBCT images using the Dolphin Imaging software (version 11; Dolphin Imaging & Management Solutions, Chatsworth, Calif). Before the measurement, all images were standardized in orientation with the hard-palatal plane (PP plane) paralleled to the horizontal plane.

Table 1 Cephalometric landmarks and measurements used in this study

landmarks	Definition
N	Nasion: the anterior point of the intersection between the nasal and frontal bones
S	Sella: the center of the hypophyseal fossa, determined by inspection
SN Plane	SN Plane: the line connecting the point S to N
ANS	Anterior nasal spine
PNS	Posterior nasal spine
PP plane	Palatal plane: the line joining anterior nasal spine with posterior nasal spine
A	Subspinale: the most posterior point on the exterior ventral curve of the maxilla between the anterior nasal spine and Supradentale
B	Supraemental: the most posterior point on the bony curvature of the mandible between Infradentale and Pogonion
Pg	Pogonion: the most anterior point of mandibular symphysis
Me	Menton: the most inferior point on the symphysis of the mandible
Go	Constructed Gonion: bisecting the angle formed by the tangents to the lower and the posterior borders of the mandible
Mandibular plane (MP)	Mandibular plane: the line connecting the point Go to Me
H	Hyoidale: the most superior and anterior point on the body of the hyoid bone

Table 1 Continued.

landmarks	Definition
U1	Maxillary central incisor
L1	Mandibular central incisor
Mandibular position	
Mp-SN angle, °	Angle between MP plane and SN plane
SNB angle, °	Angle between point B and S at N, representing the position of the mandible in relation to the cranium
ANS-Me, mm	Lower face height. Perpendicular distance between point ANS and Me to PP plane
Maxillary position	
SNA angle, °	Angle between point A and S at N, representing the position of the maxilla in relation to the cranium
Dental structures	
U1-APg, mm	Perpendicular distance between from the tip of maxillary incisor to A-Pg line
U1-SN angle, °	Angle between the long axis of U1 and SN plane
L1-APg, mm	Perpendicular distance between from the tip of mandibular incisor to A-Pg line
L1-Mp angle, °	Angle between the long axis of L1 and MP plane
Overjet, mm	Anteroposterior overlap of U1 and L1
Overbite, mm	Superior-inferior overlap of U1 and L1
Hyoid position	
H-Mp, mm	Perpendicular distance from H to MP plane

Because the primary aim of this study was to investigate the changes of the mandibular position, 3 variables related to the mandible (Mp-SN angle, SNB angle, ANS-Me distance) were primary outcome variables. Mp-SN angle is the angle between the mandibular plane (MP plane) and sella-nasion plane (SN plane), which is typically used to represent the mandibular rotation [6,8,9]. SNB angle is the angle between point supraemental (B) and sella (S) at nasion (N) to represent the horizontal position of the mandible. ANS-Me distance is the perpendicular distance to PP plane between point anterior nasal spine (ANS) and Menton (Me) to represent the vertical position of the mandible. Other craniofacial and dental measurements were the secondary outcome variables.

The upper airway dimensions were measured before and after treatment using the Dolphin Imaging software. Before the measurement, all images were also standardized in orientation with PP plane paralleled to the horizontal plane. All planes used to define the upper airway boundary were parallel to PP plane.

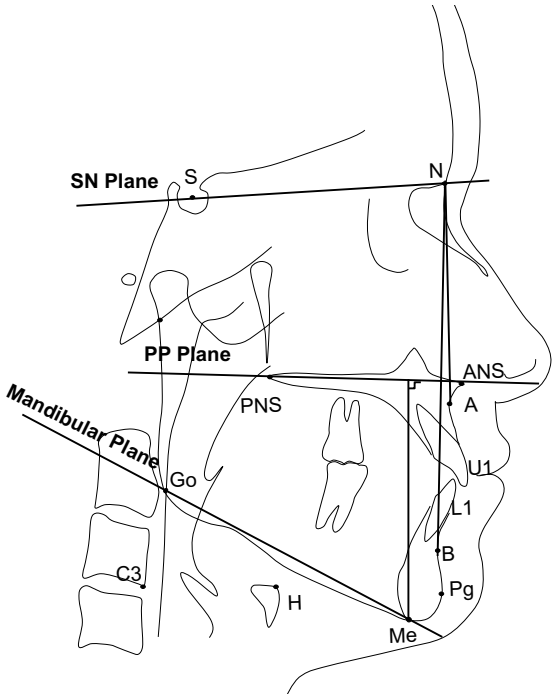

Fig. 1 Cephalometric landmarks and measurements identified on lateral cephalometric image. Mp-SN angle: angle between mandibular plane (MP) and SN plane; SNB angle: angle between point B and S at N; ANS-Me distance: perpendicular distance to PP plane between point ANS and Me. For secondary outcome variables definitions, refer to Table1

The upper airway was segmented into 2 parts according to the manual segmentation in midsagittal view: retropalatal airway and retroglossal airway. The volume of retropalatal airway and retroglossal airway was calculated automatically in cubic millimeters (mm^3) by Dolphin software after giving the boundaries. The retropalatal airway was limited superiorly by a horizontal plane crossing the PP plane, and inferiorly by a horizontal plane crossing the most posteroinferior point of the soft palate. The retroglossal airway was limited superiorly by a horizontal plane crossing the most posteroinferior point of the soft palate, and inferiorly by a horizontal plane crossing the most superior point of the epiglottis (**Fig. 2**).

The minimum cross-sectional area of the upper airway (CSA_{min}) is the most constricted axial area of the airway. By using the upper boundary of the retropalatal airway (PP plane) and the lower boundary of the retroglossal airway (the plane passing most superior point of the epiglottis), the CSA_{min} can be automatically identified and calculated by Dolphin software in square millimeters (mm^2) (**Fig. 2**).

According to a previous review [24], CSA_{min} might be the most relevant anatomic characteristic of the upper airway related to the pathogenesis of OSA. Therefore, CSA_{min} was the primary outcome variable for the upper airway dimensions and the volume of the retropalatal and retroglossal airway were the secondary outcome variables.

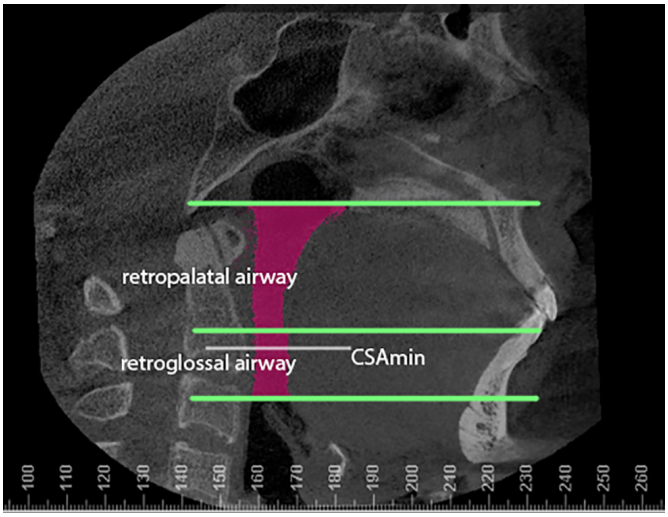

Fig. 2 Segments of the upper airway on midsagittal CBCT image using Dolphin software (Dolphin Imaging & Management Solutions, Chatsworth, Calif). Retropalatal airway: from the plane of ANS-PNS to the plane crossing the most posteroinferior point of the soft palate; retroglossal airway: from the plane crossing the most posteroinferior point of the soft palate to the plane crossing the most superior point of the epiglottis. Minimum cross-sectional area of upper airway (CSA_{min}) was automatically identified and calculated by the Dolphin software

Whether the data was normally distributed or not was tested by the Shapiro-Wilk test. Pretreatment outcome variables were compared with posttreatment outcome variables using a paired *t* test for the normally distributed variables, and Wilcoxon signed rank test for the nonnormally distributed variables. The Bonferroni-Holm method was used to correct for the increased risk of Type I error because of multiple statistical comparisons for the secondary outcome variables [25]. Pearson correlation coefficient was calculated to determine the relation between the change in CSA_{min} (ΔCSA_{min}) and changes in mandibular position (ΔMp-SN angle, ΔSNB angle, and ΔANS-Me distance). The significance level was set at $P < 0.05$. Statistical analysis was performed using SPSS software (version 24; IBM, Armonk, NY). A post-hoc power analysis was conducted to assess the power of the outcome variables using the software G*power (version 3.1.9, Franz Faul, Universität Kiel, Germany).

3. Results

Twenty-one patients who fulfilled the inclusion criteria were selected from approximately 400 orthodontic treatment recordings. Of those, 3 patients were excluded because of temporomandibular joint disorders (n = 2) and previous orthodontic treatment (n = 1). Finally, a total of 18 patients' records (mean ± standard deviation age = 21.2 ± 2.9 years), including 11 females and 7 males, were enrolled in analysis. All patients achieved the treatment goal of Class I canine and/or molar relationship with improved vertical excess and convex facial profile.

The primary outcome variables of the upper airway dimensions and mandibular position at pretreatment and posttreatment are described in **Table 2**. After treatment, the CSA_{min} significantly increased by 47.2 mm^2 (t = -2.26, P = 0.04) compared with baseline measurements. The Mp-SN angle significantly reduced by 0.9° (t = 2.20, P = 0.04), which indicated the counterclockwise rotation of the mandible. Besides, the SNB angle significantly increased by 1.2° (t = -4.30, P = 0.00), and ANS-Me significantly decreased by 1.3 mm (Z = -1.98, P = 0.05), which respectively represented the horizontal and vertical mandibular movement component of the counterclockwise rotation of the mandible.

Table 2 Primary and secondary outcome variables of the upper airway and craniofacial structures at pretreatment and posttreatment (n = 18)

Outcome variables	Pretreatment	Posttreatment	*t* or *Z*	*P* value
Primary variables				
CSA_{min}, mm^2	219.14 ± 97.20	266.31 ± 111.63	t = -2.26	0.04*
Mp-SN, °	45.25 ± 5.04	44.39 ± 5.82	t = 2.20	0.04*
SNB, °	75.89 ± 5.38	77.06 ± 5.89	t = -4.30	0.00*
ANS-Me, mm	66.75|69.00|70.00	63.63|67.00|69.25	Z = -1.98	0.05*
Secondary variables				
Upper airway volume				
Retropalatal airway, mm^3	12626.51 ± 4098.88	12580.72 ± 3979.81	t = 0.08	0.94
Retroglossal airway, mm^3	5916.49 ± 2041.66	7130.12 ± 3080.86	t = -1.80	0.09
Maxillary position				
SNA, °	81.61 ± 6.21	82.22 ± 6.69	t = -1.88	0.08
Dental structure				
U1-APg, mm	12.36 ± 2.31	9.36 ± 1.76	t = 7.14	0.00*
U1-SN, °	108.06 ± 6.58	104.42 ± 5.59	t = 2.85	0.01
L1-APg, mm	6.18 ± 2.55	4.89 ± 2.37	t = 2.19	0.04
L1-Mp, °	96.36 ± 6.88	94.56 ± 8.93	t = 1.43	0.17
Overjet, mm	5.37 ± 2.41	4.39 ± 1.53	t = 2.54	0.02
Overbite, mm	1.59 ± 1.04	2.30 ± 1.18	t = -2.19	0.04

Table 2 Continued.

Outcome variables	Pretreatment	Posttreatment	*t* or *Z*	*P* value
Hyoid position				
H-Mp, mm	8.98|18.40|40.15	9.18|14.65|32.05	*Z* = -0.46	0.65

Note. Normally distributed variables are presented as means and standard deviations; non-normally distributed variables are presented as 25 percentiles|median|75 percentiles; *t*, paired *t* test; *Z*, Wilcoxon signed rank test. For primary variables: * statistically significant at the 0.05 probability level; for secondary variables: * statistically significant after Bonferroni–Holm correction

CSA_{min}, minimum cross-sectional area of upper airway; *Mp-SN angle*, angle between Mandibular plane (MP) and SN plane; *SNB angle*, angle between point B and S at N; *ANS-Me distance*, perpendicular distance between point ANS and Me to PP plane. For secondary outcome variables definitions, refer to Table1

The secondary outcome variables of the upper airway dimensions and craniofacial structures at pretreatment and posttreatment are also described in **Table 2**. There was no significant change in the volume of retroglossal and retropalatal airway (*P* = 0.09-0.94). The U1-APg distance significantly decreased by 3.0 mm (*t* = 7.14, *P* = 0.00), which indicated significant retraction of the maxillary incisors. No significant change was found in the SN-U1 angle, mandibular incisor position, overbite, overjet, and hyoid position after Bonferroni-Holm correction (*P* = 0.01-0.65).

The correlation between the change of the CSA_{min} (ΔCSA_{min}) and the changes of the mandibular position (ΔMp-SN, ΔSNB, and ΔANS-Me) are presented in **Table 3**. ΔCSA_{min} showed a significant correlation with the ΔANS-Me (*r* = -0.60, *P* = 0.01), while it did not show a significant correlation with the ΔMp-SN angle (*P* = 0.25) and the ΔSNB angle (*P* = 0.11). Thus, the increase of CSA_{min} had a significant relation with the upward movement of the mandible.

Table 3. Correlations between the change of the CSA_{min} (ΔCSA_{min}) and the change of the mandibular position (ΔMp-SN angle, ΔSNB angle and ΔANS-Me distance) (*n* = 18)

Airway variables	Mandibular variables	*r*	*P* value
ΔCSA_{min}, mm^2	ΔMp-SN, °	-0.28	0.25
	ΔANS-Me, mm	-0.60	0.01*
	ΔSNB, °	0.38	0.11

CSA_{min}, minimum cross-sectional area of upper airway; *Mp-SN angle*, angle between Mandibular plane (MP) and SN plane; *SNB angle*, angle between point B and S at N; *ANS-Me distance*, perpendicular distance between point ANS and Me to PP plane. *Statistically significant at the 0.05 probability level

4. Discussion

The primary aim of this study was to investigate the effects of miniscrew-assisted orthodontic extraction treatment on upper airway dimensions and mandibular position in adult patients with Class II high-angle malocclusion. The secondary aim was to investigate the correlation between the changes of upper airway dimensions and the changes of mandibular position. The results indicated that with the miniscrews to intrude molars, the mandible rotated counterclockwise significantly, and the upper airway dimensions increased significantly after treatment. Furthermore, the increase of the CSA_{min} of the upper airway was significantly correlated with the upward movement of mandible.

The intrusion of a molar needs skeletal anchorage, which is difficult to achieve with traditional orthodontic techniques such as multibrackets combined with intra- or extraoral anchorage [4]. The use of titanium miniplates [8,9] or miniscrews [4] as orthodontic anchorage devices can significantly intrude the molars, resulting in counterclockwise rotation of the mandible and decrease the facial height. In our study, miniscrews were used as skeletal anchorage to intrude maxillary molars. After treatment, the mandible significantly rotated counterclockwise by 0.9° ($P = 0.04$) and anterior facial height significantly decreased by 1.3 mm ($P = 0.05$). The movement of the mandible in our study is similar to the one found in a previous study by Oliveira et al. [26]. In their study, titanium miniplates were adjusted to the zygomatic buttress to intrude the maxillary posterior teeth, which resulted in counterclockwise rotation of mandible by 1.6˚ and in a decrease of anterior facial height by 1.8 mm. However, compared with miniplate, miniscrew does not require a flap, and, thus, is easier to use in a clinic [27]. Besides, in the retention phase, the screws were easily removed with a screwdriver. Therefore, miniscrews were used in this study.

When treating patients with a severe open bite, some studies intruded the molars in both maxilla and mandible, which resulted in around 3° counterclockwise rotation of mandible [6,28]. Compared with the maxilla with its thin cortices and trabecular bone, the mandible is composed of thick cortices and more radially oriented trabeculae. Consequently, intrusion of molars in the mandible has a larger relapse tendency in 2-year follow-up than that of molars in the maxilla [28]. Moreover, compared with patients with a severe open bite, patients with Class II high-angle malocclusion need less mandibular counterclockwise rotation. Thus, we intruded molars only in the maxilla in this study.

By the upward component of the counterclockwise rotation, the lower facial height reduced by 1.3 mm. Besides, by the forward component of the counterclockwise

rotation, the SNB angle significantly increased by 1.2°. These movements respectively eliminated the mandibular vertical excess and the convex facial profile, which improved the esthetic of patients with Class II high-angle malocclusion. However, this treatment should not be used in patients with Class III malocclusion or patients with a low-angle from the point of esthetics.

Despite successful results in the counterclockwise rotation of mandible, it is unclear whether this outcome will be maintained in the long-term follow-up. A study by Baek et al. [29] concluded that the intrusion of the maxillary molar relapsed significantly at the 3-year follow-up. However, they also found that appropriate retention method during this period can clearly enhance the long-term stability of the treatment outcome. Further study with long-term follow-up will give a better understanding of the risk of relapse in the long-term.

The human airway increases in length and volume during a rapid period of craniofacial growth in patients between the ages of 8 and 18 years [30]. Rapid growth of the airway may influence the effect of orthodontic treatment, and different growth rates in adolescent patients may further complicate the interpretation of the effect of orthodontic treatment [31]. In order to eliminate the potential effects of growth on upper airway dimensions, only adult patients were included in the present study.

In the present study, the CSA_{min} significantly enlarged by 47.2 mm^2 after treatment, and the increase of CSA_{min} was significantly related to the upward movement of the mandible. A post-hoc power calculation was performed to explain the power of this study. The effect size for the change of CSA_{min} was 0.53, which shows that we achieved a power of around 57% with our study sample. Further, the effect size of the correlation between the ΔCSA_{min} and ΔANS-Me was 0.60, which shows that we achieved a power around 80%, which could be considered as adequate [32]. In the study by Zhang et al. [5], the dimensions of the upper airway in patients with Class II high-angle malocclusion did not significantly change after orthodontic premolar extraction treatment based on CBCT images. However, in that study, there was no strategy mentioned to intrude maxillary molars during the treatment, and no results were provided regarding the mandibular position changes after treatment. The different mandibular position change between our study and the study by Zhang et al. [5] could explain the different results in upper airway dimensions.

An association could be expected between the upper airway dimensions and the mandibular position, including the sagittal pattern [33] and vertical pattern [34] of the mandible. Furthermore, it was suggested that the vertical pattern of the

mandible may have a stronger effect on upper airway dimensions than sagittal pattern. The study by Oz et al. [35] showed that airway space measurements in low- and neutral-angle Class II subjects did not differ from those of a skeletal Class I control group, while the high-angle group's upper airway space was significantly smaller. It is a general assumption that there is mutual interaction between the upper airway dimension and the mandibular position during growth and development through the muscular balance [36]. Besides, it has been demonstrated that mouth opening is associated with a significant decrease in upper airway airspace [37,38]. The possible mechanism would be that downward movement of the mandible is associated with posterior displacement of the soft tissues surrounding the airway [39] and reductions in the retroglossal airspace [40].

However, to the best of our knowledge, no previous study has investigated the effects of upward movement of the mandible on the upper airway dimensions. In the present study, there was a significant correlation between the upper airway enlargement and the upward movement of the mandible. We speculated that the upward movement of the mandible could lift the tongue upward and decrease the tongue volume in the anteroposterior direction. Because the anterior wall of the upper airway comprises the tongue tissue, the decrease in the tongue volume in the anteroposterior direction could increase the upper airway dimensions. This may be an explanation as to why the upward movement of the mandible increased the upper airway dimensions in the present study.

The study by Galvin et al. [41] concluded that the average CSA_{min} for OSA patients was 67.1 mm^2, whereas the control subjects had a mean value of 177.8 mm^2. According to Tso et al. [42], the range of the CSA_{min} in healthy adults varies from 90 to 360 mm^2. In our study, the mean CSA_{min} after treatment was 266.3 mm^2, with a range of 116.4 to 487.5 mm^2, which represents a normal population. Although a small CSA_{min} is the most relevant anatomic characteristic of the upper airway related to the pathogenesis of OSA [24], there are multiple causes or "phenotypic traits" that contribute to the pathogenesis of OSA. These traits include, besides anatomic (narrow upper airway), also nonanatomic (waking up too easily during airway narrowing [a low respiratory arousal threshold], ineffective or reduced pharyngeal dilator muscle activity during sleep, and unstable ventilatory control [high loop gain]) components [43]. The contribution of these traits to OSA pathogenesis varies between patients [43]. Therefore, we hypothesize that the increase in CSA_{min} as a result of our orthodontic treatment protocol may be beneficial in decreasing the risk for OSA in only a part of our patient group. In contrast, a decrease in CSA_{min} as a result of an orthodontic treatment does not necessarily result in a higher risk for OSA in all patients.

The present study had a potential limitation in generalizability of our research outcomes as all the outcome variables were measured by a single experienced examiner to limit the bias of interexaminer variability in measuring CBCT variables. Further, long-term randomized controlled trials are necessary to find solid evidence for the effects of our described orthodontic treatment protocol on upper airway dimensions.

5. Conclusions

By using the miniscrews to intrude the maxillary molars, orthodontic premolar extraction treatment rotates the mandible counterclockwise and increases the upper airway dimensions in adult patients with Class II high-angle malocclusion. The increase of the upper airway dimensions is significantly related to the upward movement of the mandible.

Acknowledgements
This work was partially supported by China Scholarship Council (CSC) scholarship.

Conflict of Interest
All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. **Dr. Frank Lobbezoo** reports grants from Sunstar Suisse SA, grants from Somnomed-Goedegebuure, grants from Airway Management, outside the submitted work. **Dr. Ghizlane Aarab** reports grants from SomnoMed Goedegebuure, grants from Sunstar Suisse, outside the submitted work.

References

1. Moyers RE, Riolo ML, Guire KE, Wainright RL, Bookstein FL (1980) Differential diagnosis of Class II malocclusions: Part 1. Facial types associated with Class II malocclusions. American journal of orthodontics 78 (5):477-494
2. Ye R, Li Y, Li X, Li J, Wang J, Zhao S, Zhao Z (2013) Occlusal plane canting reduction accompanies mandibular counterclockwise rotation in camouflaging treatment of hyperdivergent skeletal Class II malocclusion. The Angle orthodontist 83 (5):758-765. doi:10.2319/101512-801.1
3. Bhatia S, Jayan B, Chopra SS (2016) Effect of retraction of anterior teeth on pharyngeal airway and hyoid bone position in Class I bimaxillary dentoalveolar protrusion. Medical journal, Armed Forces India 72 (Suppl 1):S17-s23. doi:10.1016/j.mjafi.2016.06.006
4. Kuroda S, Katayama A, Takano-Yamamoto T (2004) Severe anterior open-bite case treated using titanium screw anchorage. Angle Orthodontist 74 (4):558-567
5. Zhang J, Chen G, Li W, Xu T, Gao X (2015) Upper Airway Changes after Orthodontic Extraction Treatment in Adults: A Preliminary Study using Cone Beam Computed Tomography. PloS one 10 (11):e0143233. doi:10.1371/journal.pone.0143233
6. Kuroda S, Sakai Y, Tamamura N, Deguchi T, Takano-Yamamoto T (2007) Treatment of severe anterior open bite with skeletal anchorage in adults: Comparison with orthognathic surgery outcomes. American Journal of Orthodontics and Dentofacial Orthopedics 132 (5):599-605. doi:https://doi.org/10.1016/j.ajodo.2005.11.046
7. Sugawara J, Baik UB, Umemori M, Takahashi I, Nagasaka H, Kawamura H, Mitani H (2002) Treatment and posttreatment dentoalveolar changes following intrusion of mandibular molars with application of a skeletal anchorage system (SAS) for open bite correction. The International journal of adult orthodontics and orthognathic surgery 17 (4):243-253
8. Sherwood KH, Burch JG, Thompson WJ (2002) Closing anterior open bites by intruding molars with titanium miniplate anchorage. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics 122 (6):593-600. doi:10.1067/mod.2002.128641
9. Erverdi N, Keles A, Nanda R (2004) The use of skeletal anchorage in open bite treatment: a cephalometric evaluation. The Angle orthodontist 74 (3):381-390. doi:10.1043/0003-3219(2004)074<0381:tuosai>2.0.co;2
10. Zicari AM, Duse M, Occasi F, Luzzi V, Ortolani E, Bardanzellu F, Bertin S, Polimeni A (2014) Cephalometric pattern and nasal patency in children with primary snoring: the evidence of a direct correlation. PLoS One 9 (10):e111675. doi:10.1371/journal.pone.0111675
11. Deng J, Gao X (2012) A case--control study of craniofacial features of children with obstructed sleep apnea. Sleep & breathing = Schlaf & Atmung 16 (4):1219-1227. doi:10.1007/s11325-011-0636-4
12. Sutherland K, Lee RW, Cistulli PA (2012) Obesity and craniofacial structure as risk factors for obstructive sleep apnoea: impact of ethnicity. Respirology (Carlton, Vic) 17 (2):213-222. doi:10.1111/j.1440-1843.2011.02082.x
13. Lee RW, Vasudavan S, Hui DS, Prvan T, Petocz P, Darendeliler MA, Cistulli PA (2010) Differences in craniofacial structures and obesity in Caucasian and Chinese patients with obstructive sleep apnea. Sleep 33 (8):1075-1080
14. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force (1999). Sleep 22 (5):667-689
15. Franklin KA, Lindberg E (2015) Obstructive sleep apnea is a common disorder in the population—a review on the epidemiology of sleep apnea. Journal of thoracic disease 7 (8):1311
16. Leung RS, Douglas Bradley T (2001) Sleep apnea and cardiovascular disease. American journal of respiratory and critical care medicine 164 (12):2147-2165
17. Neelapu BC, Kharbanda OP, Sardana HK, Balachandran R, Sardana V, Kapoor P, Gupta A, Vasamsetti S (2017) Craniofacial and upper airway morphology in adult obstructive sleep apnea patients: a systematic review and meta-analysis of cephalometric studies. Sleep medicine reviews 31:79-90
18. Al Maaitah E, El Said N, Abu Alhaija ES (2012) First premolar extraction effects on upper airway dimension in bimaxillary proclination patients. The Angle orthodontist 82 (5):853-859. doi:10.2319/101711-646.1
19. Pliska BT, Tam IT, Lowe AA, Madson AM, Almeida FR (2016) Effect of orthodontic treatment on the upper airway volume in adults. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics 150 (6):937-944. doi:10.1016/j.ajodo.2016.05.013
20. Wang Q, Jia P, Anderson NK, Wang L, Lin J (2012) Changes of pharyngeal airway size and hyoid bone position following orthodontic treatment of Class I bimaxillary protrusion. The Angle orthodontist 82 (1):115-121. doi:10.2319/011011-13.1

21. Chen Y, Hong L, Wang CL, Zhang SJ, Cao C, Wei F, Lv T, Zhang F, Liu DX (2012) Effect of large incisor retraction on upper airway morphology in adult bimaxillary protrusion patients. The Angle orthodontist 82 (6):964-970. doi:10.2319/110211-675.1
22. Germec-Cakan D, Taner T, Akan S (2011) Uvulo-glossopharyngeal dimensions in non-extraction, extraction with minimum anchorage, and extraction with maximum anchorage. European journal of orthodontics 33 (5):515-520. doi:10.1093/ejo/cjq109
23. Upadhyay M, Yadav S, Nanda R (2012) Biomechanical basis of extraction space closure. Esthetics and Biomechanics in Orthodontics:108
24. Chen H, Aarab G, de Ruiter MH, de Lange J, Lobbezoo F, van der Stelt PF (2016) Three-dimensional imaging of the upper airway anatomy in obstructive sleep apnea: a systematic review. Sleep medicine 21:19-27. doi:10.1016/j.sleep.2016.01.022
25. Holm S (1979) A simple sequentially rejective multiple test procedure. Scandinavian journal of statistics:65-70
26. Oliveira TF, Nakao CY, Goncalves JR, Santos-Pinto A (2015) Maxillary molar intrusion with zygomatic anchorage in open bite treatment: lateral and oblique cephalometric evaluation. Oral and maxillofacial surgery 19 (1):71-77. doi:10.1007/s10006-014-0457-2
27. Kuroda S, Sugawara Y, Deguchi T, Kyung HM, Takano-Yamamoto T (2007) Clinical use of miniscrew implants as orthodontic anchorage: success rates and postoperative discomfort. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics 131 (1):9-15. doi:10.1016/j.ajodo.2005.02.032
28. Deguchi T, Kurosaka H, Oikawa H, Kuroda S, Takahashi I, Yamashiro T, Takano-Yamamoto T (2011) Comparison of orthodontic treatment outcomes in adults with skeletal open bite between conventional edgewise treatment and implant-anchored orthodontics. American Journal of Orthodontics and Dentofacial Orthopedics 139 (4):S60-S68
29. Baek MS, Choi YJ, Yu HS, Lee KJ, Kwak J, Park YC (2010) Long-term stability of anterior open-bite treatment by intrusion of maxillary posterior teeth. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics 138 (4):396.e391-399; discussion 396-398. doi:10.1016/j.ajodo.2010.04.023
30. Chiang CC, Jeffres MN, Miller A, Hatcher DC (2012) Three-dimensional airway evaluation in 387 subjects from one university orthodontic clinic using cone beam computed tomography. The Angle orthodontist 82 (6):985-992. doi:10.2319/122811-801.1
31. Hu Z, Yin X, Liao J, Zhou C, Yang Z, Zou S (2015) The effect of teeth extraction for orthodontic treatment on the upper airway: a systematic review. Sleep & breathing = Schlaf & Atmung 19 (2):441-451. doi:10.1007/s11325-015-1122-1
32. Di Stefano J (2003) How much power is enough? Against the development of an arbitrary convention for statistical power calculations. Functional Ecology 17 (5):707-709
33. Jena AK, Singh SP, Utreja AK (2010) Sagittal mandibular development effects on the dimensions of the awake pharyngeal airway passage. The Angle orthodontist 80 (6):1061-1067
34. BATOOL I, SHAHEED M, RIZVI SAA, Assad A (2010) Comparison of upper and lower pharyngeal airway space in class II high and low angle cases. Pakistan Oral & Dental Journal 30 (1)
35. Oz U, Orhan K, Rubenduz M (2013) Two-dimensional lateral cephalometric evaluation of varying types of Class II subgroups on posterior airway space in postadolescent girls: a pilot study. Journal of orofacial orthopedics = Fortschritte der Kieferorthopadie : Organ/official journal Deutsche Gesellschaft fur Kieferorthopadie 74 (1):18-27. doi:10.1007/s00056-012-0121-0
36. Stellzig-Eisenhauer A, Meyer-Marcotty P (2010) Interaction between otorhinolaryngology and orthodontics: correlation between the nasopharyngeal airway and the craniofacial complex. GMS current topics in otorhinolaryngology, head and neck surgery 9
37. Meurice J-C, Marc I, Carrier G, Sériès F (1996) Effects of mouth opening on upper airway collapsibility in normal sleeping subjects. American journal of respiratory and critical care medicine 153 (1):255-259
38. Vroegop AV, Vanderveken OM, Van de Heyning PH, Braem MJ (2012) Effects of vertical opening on pharyngeal dimensions in patients with obstructive sleep apnoea. Sleep medicine 13 (3):314-316
39. Watanabe T, Isono S, Tanaka A, Tanzawa H, Nishino T (2002) Contribution of body habitus and craniofacial characteristics to segmental closing pressures of the passive pharynx in patients with sleep-disordered breathing. American journal of respiratory and critical care medicine 165 (2):260-265
40. Kuna ST, Remmers JE (1985) Neural and anatomic factors related to upper airway occlusion during sleep. Medical Clinics of North America 69 (6):1221-1242
41. Galvin JR, Rooholamini SA, Stanford W (1989) Obstructive sleep apnea: diagnosis with ultrafast CT. Radiology 171 (3):775-778. doi:10.1148/radiology.171.3.2717750
42. Tso HH, Lee JS, Huang JC, Maki K, Hatcher D, Miller AJ (2009) Evaluation of the human airway using cone-beam computerized tomography. Oral surgery, oral medicine, oral pathology, oral radiology, and

endodontics 108 (5):768-776. doi:10.1016/j.tripleo.2009.05.026
43. Carberry JC, Amatoury J, Eckert DJ (2018) Personalized management approach for OSA. Chest 153 (3):744-755

Chapter 5

Comparisons of the effects of two types of titratable mandibular advancement devices on respiratory parameters and upper airway dimensions in patients with obstructive sleep apnea: a randomized controlled trial

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Published as: Shi, X., Lobbezoo, F., Chen, H., Rosenmöller, B. R. A. M., Berkhout, E., de Lange, J., & Aarab, G. (2023). Comparisons of the effects of two types of titratable mandibular advancement devices on respiratory parameters and upper airway dimensions in patients with obstructive sleep apnea: a randomized controlled trial. Clinical oral investigations, 27(5), 2013–2025. https://doi.org/10.1007/s00784-023-04945-z

Abstract

Objectives

To compare the effects of two types of titratable mandibular advancement devices (MADs), namely MAD-H (allowing limited vertical opening) and MAD-S (allowing free vertical opening), on respiratory parameters and upper airway dimensions in patients with mild to moderate obstructive sleep apnea (OSA).

Materials and Methods

Patients with mild to moderate OSA (5 ≤ apnea-hypopnea index (AHI) < 30 /h) were randomly assigned to two parallel MAD groups. All MADs were subjectively titrated according to a standardized protocol during a 3-month follow-up. Every patient underwent two polysomnographic recordings, and two cone beam computed tomography scans in supine position: one at baseline and another one after 3 months with the MAD *in situ*. The primary outcome variables were the AHI in supine position (AHI-supine) and the minimal cross-sectional area of the upper airway in supine position (CSAmin-supine).

Results

A total of 49 patients were recruited, and 31 patients (21 men and 10 women) with a mean (± SD) age of 48.5 (± 13.9) years and a mean AHI of 16.6 (± 6.7) /h completed the study. In the per-protocol analysis, there was no significant difference between MAD-H (n = 16) and MAD-S (n = 15) in their effects on AHI-supine (P = 0.14) and CSAmin-supine (P = 0.59). Similar results were found in the intention-to-treat analysis (P = 0.47 and 0.57, respectively).

Conclusions

Within the limitations of this study, we conclude that there is no significant difference in the effects of an MAD allowing limited vertical opening and an MAD allowing free vertical opening on respiratory parameters and upper airway dimensions in patients with mild to moderate OSA.

Keywords

Obstructive sleep apnea, Mandibular advancement device, Freedom of mandibular vertical opening, Cone beam computed tomography, Upper airway dimensions

1. Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent obstructions of the upper airway, often resulting in oxygen desaturations and arousals from sleep [1]. Excessive daytime sleepiness and fatigue, lack of concentration, and loud snoring reported by the patient's bed partner are frequently reported complaints [2,3]. Furthermore, patients with untreated OSA are at increased risk of, amongst others, hypertension, stroke, heart failure, diabetes, and involvement in car accidents [4-7]. The diagnosis of OSA relies on the combination of symptoms, clinical signs, and objective assessment of obstructive respiratory events. The gold standard for assessing respiration during sleep in patients with OSA is full-night polysomnography (PSG). One commonly used indicator of OSA severity is the number of respiratory events (apneas and/or hypopneas) per hour of sleep during PSG recording, viz., apnea-hypopnea index (AHI). An adult showing an AHI of at least 5 events/hour is diagnosed with OSA [1]. Based on the AHI, OSA severity for adults is classified as mild ($5 \leq AHI < 15$ events/hour), moderate ($15 \leq AHI \leq 30$ events/hour), or severe (AHI > 30 events/hour) [1].

Continuous positive airway pressure (CPAP) is the most efficacious therapy for OSA [8]. However, the equipment is relatively cumbersome, which results in low compliance of patients [9]. Alternatively, mandibular advancement device (MAD) therapy is recommended as a primary treatment option in patients with mild and moderate OSA, and in patients with severe OSA who refuse or are unable to tolerate CPAP therapy [10-12].

There is a large variety of commercially available customized MADs. Over the years, the customized MAD has evolved from the "mono-bloc" type of appliance, which consists of a single piece giving the mandible a fixed position, towards the current "bi-block titratable" type, which consists of two separate pieces that are dynamically interconnected allowing different degree of lateral and/or vertical movements. Understanding the treatment efficacy and working mechanism of MADs with different design features has an ongoing interest in the clinic [13,14]. Previous studies [15-19] suggested that mono-block MADs may have higher effectiveness than bi-block titratable MADs because the mandible is protruded firmly. However, a bi-block titratable MAD is more comfortable for patients as it allows some degree of mandibular movement and has higher compliance [19]. Besides, it is easier and takes less time to titrate a bi-block titratable MAD to the optimal mandibular position. Therefore, bi-block titratable MADs are increasingly recommended [20].

Bi-block titratable MADs may differ in the freedom of mandibular vertical opening. There are two types of bi-block titratable MADs that are commonly used in the treatment of OSA: the Herbst appliance (MAD-H) and the SomnoDent appliance (MAD-S). They predominantly differ in the freedom of vertical opening: the MAD-H only allows limited vertical opening, while the MAD-S allows free vertical opening of the mandible during sleep. A retrospective study suggested no significant difference between MAD-H and MAD-S in changing the AHI [21]. However, that study was not randomized, and therefore the outcomes may be biased. As most previous studies focused on the comparisons between mono-bock MADs and bi-block MADs, comparisons of bi-block MADs with different freedom of mandibular vertical opening are limited. Therefore, more evidence is needed on the comparison between these two types of MAD.

The working mechanism of MAD is related to the improvement of the upper airway dimensions through mandibular protrusion [22-24]. On the other hand, mouth opening is unavoidable with MAD *in situ*, which may decrease the beneficial effects on the volume and the cross-sectional area (CSA) of the upper airway [25-27]. A systematic review study [28] has suggested that a small minimal cross-sectional area of the upper airway (CSAmin) is the most relevant anatomical characteristic of the upper airway related to the pathogenesis of OSA. However, when comparing different MADs, few studies have provided insights into their effects on the upper airway dimensions using three-dimensional images. The investigations on upper airway dimensions may allow better understanding of the working mechanism of MAD and help to explain the different treatment efficacy between MADs.

We hypothesized that MAD-H (allowing limited vertical opening) would lead to better improvement in respiratory parameters and upper airway dimensions compared to MAD-S (allowing free vertical opening), especially in supine position. This hypothesis was based primarily on the notion that gravity may promote more mandibular opening in the MAD-S group in the supine position, which subsequently results in less improvement of the upper airway CSAmin [25,26] and AHI-supine [29,30] compared with the MAD-H group. Therefore, the aim of this randomized controlled trial (RCT) was to compare the effects of MAD-H and MAD-S on respiratory parameters and upper airway dimensions in patients with mild to moderate OSA.

2. Material and methods

2.1 Overview

This study was a multi-center RCT with a parallel design, in which the effects of two types of titratable MADs on respiratory parameters and upper airway dimensions were compared. The allocation sequence was automatically generated through an electronic data capture system (Castor EDC), using random block size of either 4, 6, or 8 with an allocation ratio of 1:1. The Medical Research Ethics Committee of the Academic Medical Center Amsterdam (AMC) approved this study (#: NL44085.018.13). The study was registered at clinicaltrials.gov (ClinicalTrials.gov identifier: NCT02724865). Written informed consent was obtained from all participants.

2.2 Participants

Eligible patients, diagnosed with OSA at four sleep centers in the Netherlands (Onze Lieve Vrouwe Gasthuis Ziekenhuis (OLVG), Nederlands Slaap Instituut, Medisch Centrum Jan van Goyen, and AMC), were referred to the department of Oral and Maxillofacial Surgery of AMC to participate in the present study. The inclusion criteria were: 1. ≥18 years old; 2. ability to speak, read, and write Dutch; 3. ability to follow-up; 4. ability to use a computer with internet connection for online questionnaires; 5. diagnosis with symptomatic mild or moderate OSA (5 ≤ apnea-hypopnea index (AHI) < 30 events/hour) with at least two OSA symptoms (e.g., snoring, fragmented sleep, witnessed apneas, and/or excessive daytime sleepiness determined by Epworth Sleepiness Scale (ESS) [1]); and 6. expected to maintain current lifestyle (e.g., sports, medicine, diet, etc.). The exclusion criteria were: 1. untreated periodontal problems, dental pain, and/or a lack of retention possibilities for an MAD; 2. medication usage that could influence respiration or sleep; 3. evidence of respiratory/sleep disorders other than OSA (e.g., central sleep apnea syndrome); 4. systematic disorders based on medical history and examination (e.g., rheumatoid arthritis); 5. severe temporomandibular disorders based on a functional examination of the masticatory system; 6. coexistence of non-respiratory sleep disorders (e.g., insomnia, periodic limb movement disorder, or narcolepsy); 7. known medical history of mental retardation, memory disorders, or psychiatric disorders; 8. reversible morphological upper airway abnormalities (e.g., enlarged tonsils, deviated nasal septum, and/or inferior nasal turbinate hypertrophy); 9. inability to provide informed consent; 10. simultaneous use of other modalities to treat OSA; and/or 11. previous treatment with an MAD.

2.3 MADs

The two types of MAD compared in this study were MAD-H (Herbst appliance;

4Dental labs, Amsterdam, the Netherlands) and MAD-S (SomnoDent appliance; SomnoDent Flex, SomnoMed, Sydney, Australia). The MAD-H consisted of two splints connected to each other with adjustable iron-bars for titration. The vertical opening was limited by these bars (**Fig. 1A**). The MAD-S consisted of two separate splints allowing free vertical opening. It had a screw mechanism on the upper splint which was used for titration (**Fig. 1B**).

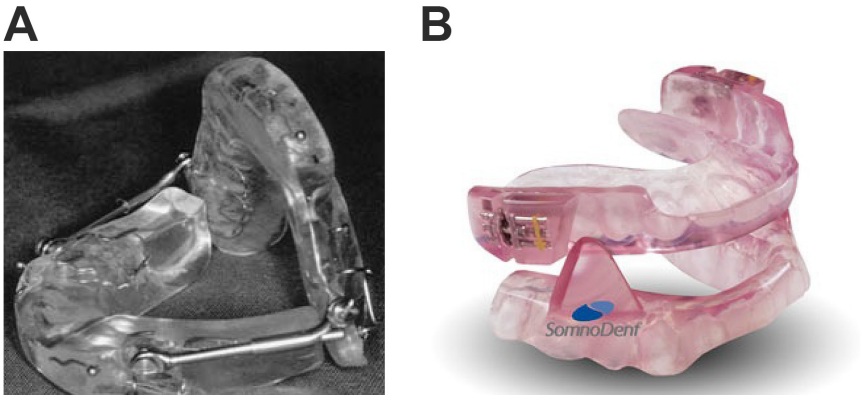

Fig. 1 Mandibular advancement devices (MADs). **A.** MAD-H (Herbst appliance; 4Dental labs, Amsterdam, the Netherlands). **B.** MAD-S (SomnoDent appliance; SomnoDent Flex, SomnoMed, Sydney, Australia)

The standardized titration [31] of the MAD was performed at the department of Orofacial Pain and Dysfunction of the Academic Centre for Dentistry Amsterdam (ACTA) for the MAD-S, and the department of Oral and Maxillofacial Surgery of AMC for the MAD-H. All MAD providers were trained for the standardized titration protocol before the start of the study. After adequate assessment of the central relation and maximum protrusion using the George Gauge system with a standard 5-mm vertical dimension (Great Lakes Orthodontics, Tonawanda, NY), MADs were set at 60% of the maximal mandibular protrusion at baseline [31]. The patient returned to the clinic at 4, 8, and 12 weeks after placement of the MAD for titration. At each consecutive visit, the MADs were evaluated and advanced to 75% and 90% if subjective improvement (e.g., perceived reduction of snoring or excessive daytime sleepiness) of OSA was not reached. On the other hand, if side effects were not acceptable for the patient (e.g., tooth pain or signs of temporomandibular disorders), the advancement was adjusted backwards in steps of 15% per visit to 75%, 60%, or 45%, depending on the actual position at the time of the clinical visit. No adjustments were made when the patient reported sufficient efficacy without side effects.

2.4 MAD side-effects and compliance

The self-reported side effects were recorded at each clinical visit, including the following: 1. sensitive teeth in the morning; 2. painful jaw muscles; 3. painful temporomandibular complaints; and 4. changed occlusion in the morning. The compliance information was collected by a telephone survey, which consisted of four questions: 1. number of hours of MAD use per night; 2. number of hours of total sleep per night; 3. number of days of MAD use per week; and 4. the overall level of satisfaction of the MAD usage. Level of satisfaction was based on a visual analogue scale of 0 to 100, where 0 was unsatisfied, and 100 was very satisfied. The compliance data were expressed as percentage of hours of MAD use per total sleep time, and as percentage of days of MAD use per week.

2.5 Polysomnography (PSG) recordings

Every patient underwent a baseline PSG recording and a 3-month follow-up PSG recording with MAD *in situ* at one of the afore-mentioned sleep centers. A digital PSG system (Embla A_{10}, Broomfield, CO, USA) was used and recorded electroencephalogram (EEG) (FP2-C4/C4-O2), electrooculogram (EOG), electrocardiogram (ECG), and submental and anterior tibial electromyogram (EMG). Nasal airflow was measured by a nasal pressure cannula, and blood oxygen saturation was measured by finger pulse oximetry. Straps containing piezoelectric transducers recorded thoracoabdominal motion, and a position sensor (Sleepsense, St Charles, IL, USA) attached to the midline of the abdominal wall was used to differentiate between supine, prone, right lateral, left lateral, and upright positions [32,33].

Sleep and respiration were analyzed following the criteria of the American Academy of Sleep Medicine (AASM) Task Force [34]. All polysomnographic variables were scored manually by scorers blinded to the MAD type. Sleep outcome variables included total sleep time (TST), time spent stage N1, stage N2, stage N3, and stage rapid-eye-movement (REM), time spent in supine position, and arousal index. An apnea was defined as the cessation of oronasal airflow of more than 90% for a period of ≥10 s in the presence of respiratory efforts. A hypopnea was scored whenever there was a > 30% reduced oronasal airflow for at least 10 s, accompanied by ≥ 3% oxygen desaturation from pre-event baseline or an arousal. Respiratory outcome variables included AHI, AHI-supine, AHI-non-supine, and oxygen desaturation index (ODI). Responders were defined as ≥ 50% reduction in baseline AHI with a residual AHI < 10 events/h at the time of therapy evaluation; otherwise, patients were regarded as non-responders [35]. In this study, the AHI-supine was considered as the primary outcome variable for the respiration.

2.6 Cone beam computed tomography (CBCT)

All patients underwent two CBCT scans (NewTom 5G, QR systems, Italy) at the department of Oral Radiology of ACTA: a baseline scan and a follow-up scan with the MAD *in situ* (in the same protrusion position as during the follow-up PSG recording). The exposure settings were 110 kV, 4 mA, 0.3 mm voxel size, 3.6-s exposure time (pulsed radiation), and 18-36-s scanning time, depending on the size of the patient [36]. At baseline, patients were instructed to maintain light contact between the molars in natural occlusion, while at the follow-up scan, patients were instructed to relax their masticatory muscles with the MAD *in situ*. CBCT scans were performed in supine position while patients were awake. The head of the patient was positioned with the Frankfort horizontal plane (a plane joining the anatomical landmarks porion (Po) and orbitale (Or)) being perpendicular to floor. After scanning, further standardization of head position was performed, during which the palatal plane (anterior nasal spine (ANS)-posterior nasal spine (PNS)) was adjusted to be parallel to the horizontal plane in the sagittal view and perpendicular to the horizontal plane in the axial view [36].

Using Amira® software (v4.1, Visage Imaging Inc., Carlsbad, CA, USA), upper airway segmentation was performed by applying the superior and inferior boundaries of the upper airway. The superior boundary of the upper airway was the palatal plane, and the inferior boundary was the horizontal plane across the base of the epiglottis (parallel to the palatal plane) (**Fig. 2A**). After upper airway segmentation, the upper airway volume (V) and the cross-sectional area (CSA) of each slice were calculated automatically in the software. Based on the results of CSA, the minimum CSA(CSAmin) could be identified and located (**Fig. 2B**). On the specific slice where the CSAmin was located, the anterior-posterior dimension (A-P) and lateral dimension (La) of CSAmin were measured by the observer, using the linear measuring tool integrated in the software (**Fig. 2C**). The length of upper airway (L) was calculated by multiplying the slice numbers of the upper airway with 0.3mm (the thickness of every slice) [36]. As a small CSAmin is the most relevant anatomical characteristic of the upper airway related to the pathogenesis of OSA [28], the CSAmin was selected as the primary outcome variable of upper airway dimensions.

All of the upper airway variables were measured by an experienced examiner. To test the intra-rater reliability of the assessment of the upper airway, 10 CBCT scans were randomly selected and re-measured after a 1-month interval of the original measurements.

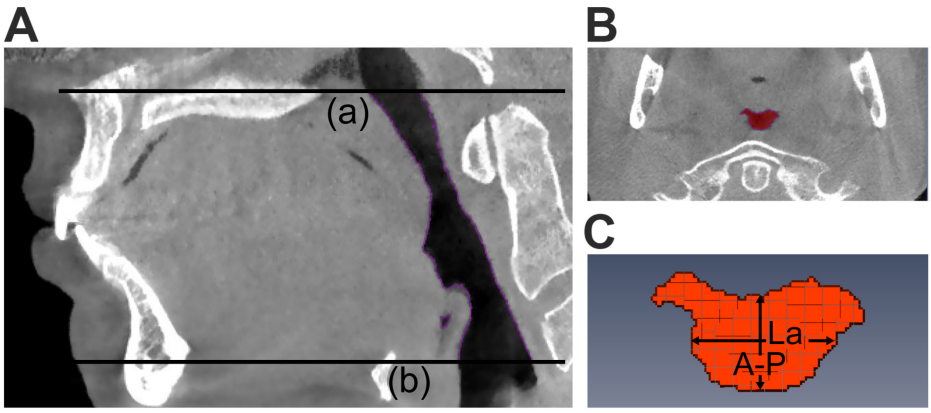

Fig. 2 Measurements of the upper airway dimensions using cone beam computed tomography (CBCT) imaging. **A.** The boundaries of the upper airway from the hard palate (a) to the base of the epiglottis (b) in the sagittal plane. **B.** The location of the minimal cross-sectional area of the upper airway (CSAmin) in the axial plane. **C.** The measurements of the anterior-posterior dimension (A-P) and lateral dimension (La) of the CSAmin

Based on baseline and follow-up CBCT images, the vertical opening with the MAD *in situ* was determined in two steps in 3Diagnosys ® software (v5.3.1, 3diemme, Cantu, Italy). Firstly, the overbite was measured based on baseline CBCT images (**Fig. 3A**). Secondly, the vertical distance between the tip of upper and lower incisors with the MAD *in situ* was measured based on follow-up CBCT images (**Fig. 3B**). All vertical distances were measured as the perpendicular distance to palatal plane. By adding these two values, the mandibular vertical opening with MAD *in situ* was determined.

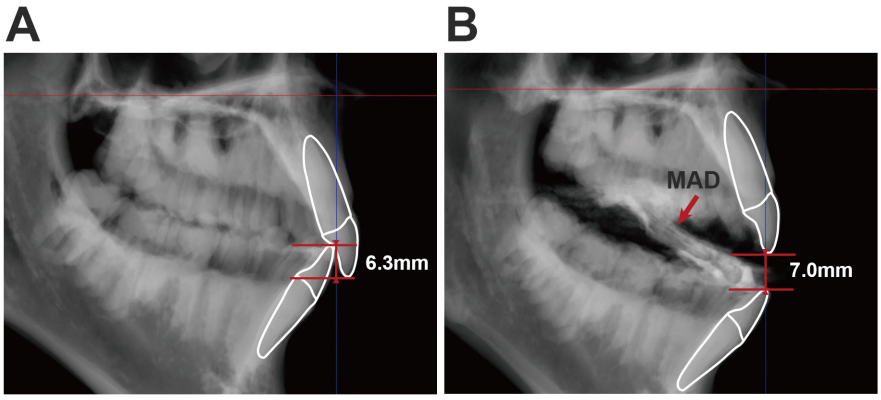

Fig. 3 Measurements of mandibular vertical opening using cone beam computed tomography (CBCT) imaging. **A.** Measurement of overbite (6.3mm in this example). **B.** Measurement of the vertical distance between the tip of upper and lower incisors with MAD *in situ* (7.0mm in this example). In this case, the vertical opening with MAD *in situ* is 13.3mm (i.e., sum of the 6.3mm and 7.0mm)

2.7 Sample size

According to the guidelines of Cohen, an effect size d, which is defined as a standardized difference in the means of an outcome variable between two groups, of 0.20 is small, one of 0.5 is medium, and one of 0.8 is large [37]. In our study, we assumed a large effect size (i.e., a large difference between both groups) based on our clinical experience. To detect the effect size d of 0.8 between two MAD groups with a power of 80% and a significance level of 5%, a sample size of about 25 patients per group is needed. Therefore, we planned to randomize 25 patients per group.

2.8 Statistical analysis

Normality of continuous data was tested by Shapiro-Wilk test. Independent *t* test (for normally distributed variables), Mann-Whitney *U* test (for non-normally distributed variables), and Chi-squared test or Fisher's exact test (for nominal variables) were used to compare the baseline characteristics, MAD titration outcomes, MAD response, MAD side-effect reports, and MAD compliance between the MAD-H group and the MAD-S group.

The intra-rater reliability for the upper airway variables was assessed using a two-way mixed, absolute agreement, single measures intraclass correlation coefficient (ICC). Reliability was defined as poor (ICC < 0.5), moderate (ICC = 0.5-0.75), good (ICC = 0.75-0.9), or excellent (ICC > 0.9) [38].

Two-way analyses of variance (ANOVA) were used to compare the mean differences of all outcome variables separately for within-subjects factor (i.e., baseline without MAD versus follow-up with MAD *in situ*), for between-subjects factor (i.e., the mean of the outcome variables of MAD-H versus MAD-S), and to assess the interaction effect between the two factors (i.e., treatment effect between baseline and follow-up of MAD-H versus MAD-S) on the outcome variables. Any significantly different baseline characteristics between both MAD groups were controlled as covariates in the assessment of the interaction effect [39]. Bonferroni-Holm method was used for the secondary outcome variables to correct for the increased risk of Type I error due to multiple statistical comparisons [40].

A per-protocol (PP) analysis included patients who completed the entire treatment and was performed for all primary and secondary outcomes variables. An intention-to-treat (ITT) analysis included all patients who underwent randomization and was performed only for the primary outcome variables. In ITT analysis, the missing data were imputed by a multiple imputation procedure (five imputed datasets) in SPSS software (SPSS version 20, Chicago, IL, USA). A *post hoc* power analysis was

conducted for the primary outcome variables using the software G*power (version 3.1.9, Franz Faul, Universität Kiel, Germany).

3. Results

3.1 Flowchart of participants

The flow-chart of 49 patients with OSA who were recruited for this study is shown in **Fig. 4**. In total, 49 patients underwent MAD randomization and were included in the ITT analysis: 26 patients in MAD-H group and 23 patients in MAD-S group. Of those patients, 10 patients in MAD-H group and 8 patients in MAD-S group were considered as dropouts for the reasons, such as lost contact, quit study, refused the second PSG recordings, and had incomplete dataset. Finally, 16 patients in MAD-H group and 15 patients in MAD-S group completed the entire study and were included in the PP analysis.

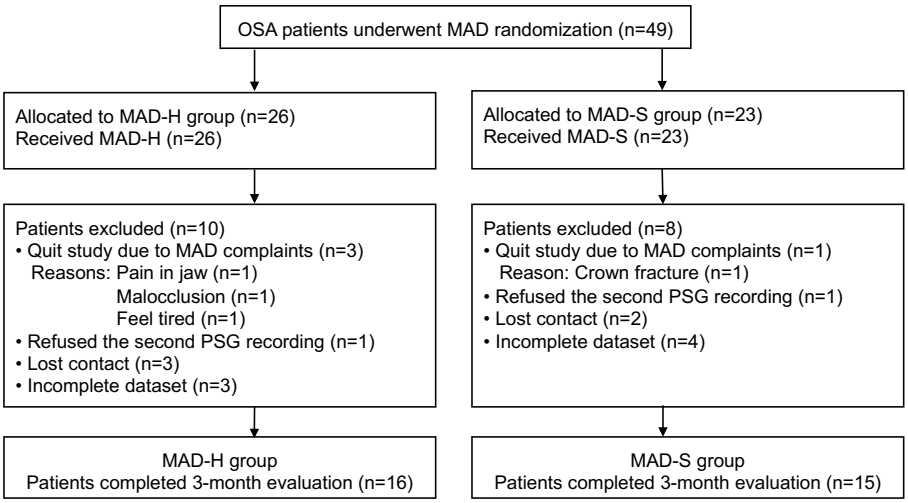

Fig. 4 Flowchart of the patients in the study. *OSA*, obstructive sleep apnea; *CBCT,* cone beam computed tomography; *PSG*, Polysomnography; *n*, sample size; *MAD,* mandibular advancement device; *MAD-H*, Herbst appliance; *MAD-S*, SomnoDent appliance

3.2 Participant characteristics

The baseline characteristics of the MAD-H group, the MAD-S group, and dropouts are shown in **Table 1**. There were no significant differences between dropouts and the participants who completed the study in age, gender distribution, body mass

index (BMI), neck circumference, and Epworth Sleepiness Scale (ESS) (P = 0.30-0.98). The MAD-H group and the MAD-S group did not significantly differ regarding gender distribution, BMI, neck circumference, and ESS (P = 0.08-1.00). However, there was a tendency that the MAD-S group (53.3 ± 15.1 years) was significantly older than the MAD-H group (44.0 ± 11.4years) (t = -1.94, P = 0.06). Therefore, age was controlled as covariate in the later analysis of comparing outcome variables between both MAD groups.

Table 1 Baseline characteristics of the MAD-H group, the MAD-S group, and dropouts

	MAD-H (n = 16)	**MAD-S (n = 15)**	**Dropouts (n = 18)**	***t/FET***	***P***
Age (years)	44.0 ± 11.4	53.3 ± 15.1	47.8 ± 12.6	-1.94 (t)	0.06
Gender (men vs women)	11 vs 5	10 vs 5	11 vs 7	FET	1.00
BMI (kg/m^2)	27.8 ± 4.6	26.5 ± 3.3	25.3|27.2|32.5	0.89 (t)	0.38
Neck circumference (cm)	40.2 ± 3.8	37.7 ± 3.8	39.3 ± 3.3	1.83 (t)	0.08
Epworth Sleepiness Scale [a]	8.6 ± 3.7	9.1 ± 3.9	8.9 ± 5.1	-0.35 (t)	0.73

Normally distributed data are shown as means ± standard deviations (SD); non-normally distributed data are presented as 25th percentile| median|75th percentile; *t,* independent *t* test; *FET,* Fisher's exact test; [a], two patients of MAD-H group, one patient of MAD-S group, and 5 patients of dropouts with incomplete ESS score were excluded from the analysis
MAD-H, Herbst appliance; *MAD-S,* SomnoDent appliance; *BMI*, body mass index

3.3 MAD use

The titration results, treatment response, side-effects, and compliance of the MAD-H and MAD-S groups are shown in **Table 2**. No significant difference was found in the mandibular protrusion and mandibular vertical opening after titration between both groups (P = 0.54-0.90). Besides, no significant difference was found in the treatment response between both groups (χ^2 = 0.03, P = 0.85). There was no significant difference between both MAD groups in the number of each side-effect (P = 0.33-1.00). Seventeen patients responded to the compliance telephone survey, and a few patients counted the wearing hours of MAD prior to their sleep, resulting in wearing hours of more than 100% of their sleep. There was no significant difference between both groups in MAD compliance and satisfaction (P = 0.08-0.40).

Table 2 The titration results, treatment response, side-effects and compliance of the MAD-H and MAD-S groups

	MAD-H (*n* = 16)	**MAD-S (*n* = 15)**	**t/Z/χ^2/FET**	***P***
Titration results				
Protrusion percentage (%)	75.0|75.0|75.0	60.0|75.0|90.0	-0.62 (Z)	0.54
Protrusion amount (mm)	8.4 ± 2.1	8.7 ± 2.3	-0.43 (t)	0.67
Vertical opening (mm)	11.3 ± 1.5	11.4 ± 1.6	-0.13 (t)	0.90
Treatment response				
Responders vs non-responders	8 vs 8	7 vs 8	0.03 (χ^2)	0.85
Side-effects				
Sensitive teeth in the morning	4	1	FET	0.33
Painful jaw muscles	3	1	FET	0.60
Painful temporomandibular complaints	3	3	FET	1.00
Changed occlusion in the morning	3	2	FET	1.00
MAD compliance	(*n* = 10)[a]	(*n* = 7)[a]		
Wearing hour (%)	100.0|107.1|127.1	100.0|100.0|100.0	-1.75 (Z)	0.08
Wearing day (%)	100.0|100.0|100.0	100.0|100.0|100.0	-0.84 (Z)	0.40
Level of satisfaction (%)	68.3 ± 24.0	77.9 ± 15.8	-0.92 (t)	0.37

Normally distributed data are shown as means ± standard deviations (SD); non-normally distributed data are presented as 25th percentile| median|75th percentile; [a], 10 patients in MAD-H group and 7 patients in MAD-S group responded to compliance telephone survey; *t,* independent t test; *Z,* Mann-Whitney U test; χ^2, Chi-squared test; *FET,* Fisher's exact test

MAD-H, Herbst appliance; *MAD-S,* SomnoDent appliance; *Wearing hour,* percentage of hours of MAD use per total sleep time, and a few patients counted the wearing hours of MAD prior to their sleep, resulting in wearing hours of more than 100% of their sleep; *Wearing day,* percentage of days of MAD use per week; *Level of satisfaction,* based on a visual analogue scale of 0 to 100, where 0 was unsatisfied, and 100 was very satisfied

3.4 Sleep and respiration

The sleep and respiratory variables without and with MAD *in situ* of the MAD-H group and the MAD-S group are presented in **Table 3**. For the primary outcome variable AHI-supine, both PP and ITT analyses indicated that there was no significant difference between MAD-H and MAD-S in improving the AHI-supine (P = 0.14 and P = 0.47, respectively). The individual effects of both MADs on AHI-supine are illustrated in **Fig. 5**. According to the *post hoc* power analysis, the effect size f of the AHI-supine was 0.29 in the PP analysis and was 0.10 in the ITT analysis (partial η^2 = 0.08 and 0.01, respectively), which is qualified as small to medium. Besides, both PP analysis and ITT analysis indicated that there was no significant change in AHI-supine with MAD *in situ* in the total group (P = 0.06 and P = 0.12, respectively). For the secondary variables, there was no significant difference between the effects of MAD-H and MAD-S (all $P > 0.05$). However, the AHI, AHI-non-supine and ODI reduced significantly with MAD *in situ* in the total group ($P < 0.01$, P = 0.01, and P = 0.02, respectively).

Table 3 The sleep and respiratory variables without and with MAD *in situ* of the MAD-H group and the MAD-S group

	MAD-H group (n = 16)		MAD-S group (n = 15)		Baseline MAD-H vs MAD-S	Within-subjects effect (Baseline vs follow-up in the total group)		Interaction effect [a] (MAD-H vs MAD-S in treatment effect)	
	Baseline	follow-up	Baseline	follow-up	*P*	*F*	*P*	*F*	*P*
Primary outcome									
AHI-supine (/h)	25.5 ± 11.6	21.8 ± 24.6	35.0 ± 17.9	23.3 ± 18.5	0.09	3.85	0.06	2.26	0.14
Secondary outcomes									
Sleep variables									
Total sleep time (min)	420.5 ± 56.6	415.6 ± 67.1	378.0 ± 63.7	388.5 ± 75.9	0.06	0.04	0.85	0.16	0.69
Stage N1 (%)[b]	9.3 ± 5.4	9.1 ± 6.6	8.2 ± 4.8	4.8 ± 3.3	0.56	2.37	0.14	2.92	0.10
Stage N2 (%)[b]	50.9 ± 7.8	48.9 ± 11.1	53.3 ± 9.6	46.9 ± 12.3	0.97	2.67	0.11	0.55	0.47
Stage N3 (%)[b]	18.6 ± 6.7	19.6 ± 7.3	17.9 ± 6.8	23.9 ± 9.8	0.79	4.14	0.05	2.10	0.16
Stage REM (%)[b]	21.1 ± 5.7	22.5 ± 6.6	20.6 ± 4.7	24.4 ± 6.8	0.78	2.33	0.14	0.65	0.43
Supine sleep time (%)	53.6 ± 33.2	48.9 ± 26.6	33.5 ± 29.8	30.0 ± 26.1	0.06	0.60	0.45	0.88	0.36
Arousal index (/h) [b]	7.6 ± 6.9	14.2 ± 14.0	12.5 ± 15.7	11.1 ± 10.6	0.50	0.62	0.44	1.30	0.27
Respiratory variables									
AHI (/h)	16.2 ± 6.1	11.4 ± 7.7	17.1 ± 7.5	11.1 ± 8.7	0.69	12.55	<0.01*	1.82	0.19
AHI-non-supine (/h)	7.1 ± 7.1	5.5 ± 4.4	12.4 ± 8.9	4.8 ± 3.3	0.07	8.49	0.01*	0.85	0.37
ODI (/h)	16.5 ± 9.7	11.0 ± 6.9	15.6 ± 10.7	12.3 ± 7.4	0.91	6.13	0.02*	0.00	0.95

Data are shown as means ± standard deviations (SD); [a], all outcome variables were controlled for age, and the variables of total sleep time, supine sleep time, and AHI-non-supine were controlled additionally for their baseline values; [b] two patients in MAD-S group with incomplete sleep dataset were excluded from the analysis of sleep variables; * significant difference after Bonferroni-Holm correction

AHI, apnea-hypopnea index; *AHI-supine,* AHI in supine position; *AHI-non-supine,* AHI in positions other than supine position; *ODI,* oxygen desaturation index; *REM,* rapid eye movement

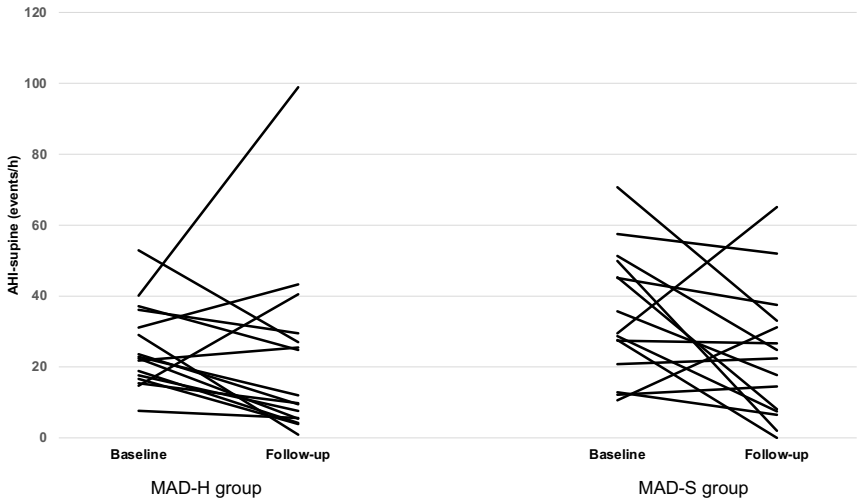

Fig. 5 The individual effects of MAD-H (n = 16) and MAD-S (n = 15) on AHI-supine. *MAD,* mandibular advancement device; *MAD-H*, Herbst appliance; *MAD-S*, SomnoDent appliance; *AHI-supine*, apnea-hypopnea index in supine position

3.5 Reliability of the upper airway assessment

The intra-rater reliability for the upper airway assessment was excellent, with ICC = 0.96 for the CSAmin and ICC = 0.90 to 0.94 for the secondary outcome variables.

3.6 Upper airway dimensions

The upper airway dimensions without and with MAD *in situ* of the MAD-H group and the MAD-S group are presented in **Table 4**. For the primary outcome variable CSAmin, both PP analysis and ITT analysis showed similar results: there was no significant difference between MAD-H and MAD-S in increasing the CSAmin (P = 0.59 and P = 0.57, respectively). According to the *post hoc* power analysis, the effect size f of the CSAmin was 0.10 in the PP analysis and was 0.08 in the ITT analysis (partial η^2 = 0.01 and 0.007, respectively), which is qualified as small. Besides, both PP analysis and ITT analysis indicated that the CSAmin increased significantly with MAD *in situ* in the total group (P = 0.01 and P < 0.01, respectively). For the secondary outcome variables, there was no significant difference between the effects of MAD-H and MAD-S (all P > 0.05). However, the lateral dimension of the CSAmin (La) increased significantly with MAD *in situ* in the total group (P < 0.01).

Table 4 Upper airway dimensions without and with MAD *in situ* of the MAD-H group and the MAD-S group

	MAD-H group (*n* = 16)		**MAD-S group (*n* = 15)**		**Baseline MAD-H vs MAD-S**	**Within-subjects effect (Baseline vs follow-up in the total group)**		**Interaction effect [a] (MAD-H vs MAD-S in treatment effect)**	
	Baseline	follow-up	Baseline	follow-up	*P*	*F*	*P*	*F*	*P*
Primary outcome									
CSAmin (mm^2)	54.8 ± 36.9	75.6 ± 50.4	58.5 ± 29.3	87.8 ± 59.1	0.50	9.13	0.01*	0.30	0.59
Secondary outcomes									
A-P (mm)	4.6 ± 2.1	5.0 ± 2.4	4.4±1.7	5.3 ± 1.9	0.77	3.37	0.08	0.35	0.56
La (mm)	11.4 ± 4.7	15.4 ± 5.1	13.1 ± 4.6	16.2 ± 5.8	0.32	16.74	<0.01*	0.12	0.74
L (mm)	67.0 ± 9.6	65.6 ± 9.9	65.9 ± 8.0	64.4 ± 8.8	0.59	4.30	0.05	0.00	0.99
V (cm^3)	10.9 ± 3.4	12.2 ± 5.5	11.4 ± 5.4	12.8 ± 5.7	0.75	3.42	0.08	0.10	0.75

Data are shown as means ± standard deviations (SD); [a], all outcome variables were controlled for age; * significant difference after Bonferroni-Holm correction
CSAmin, minimum cross-sectional area of the upper airway; *A-P,* anterior-posterior dimension of the CSAmin; *La,* lateral dimension of the CSAmin; *L,* length of the upper airway; *V,* upper airway volume

4. Discussion

The aim of this RCT was to compare the effects of MAD-H (allowing limited vertical opening) and MAD-S (allowing free vertical opening) on respiratory parameters and upper airway dimensions in patients with mild to moderate OSA. The results showed that despite differences in the freedom of mandibular vertical opening, there was no significant difference between MAD-H and MAD-S in improving the respiratory parameters and upper airway dimensions.

4.1 MAD-H vs MAD-S

In the present study, there was no significant difference between the MAD-H and MAD-S in affecting the AHI-supine, as well as AHI and AHI-non-supine. According to the *post hoc* power analysis, the effect size f of the AHI-supine was 0.29 in the PP analysis and was 0.10 in the ITT analysis, which is qualified as small to medium (an effect size f = 0.10 is small, one = 0.25 is medium, and one = 0.40 is large [37]). With this effect size, an enlargement of our total sample size to around 100-800 patients, is needed to find a statistically significant difference between both groups (with power 0.8; 5% significance level), which makes the clinical relevance of such a finding questionable. Regarding the clinical relevance of two interventions, the concept of the number needed to treat (NNT) is often used. In this study, 50% in MAD-H group and 47% in MAD-S group were treated successfully. The NNT is 33, implying that about 33 patients with mild to moderate OSA need to be treated with MAD-H to get one more successfully treated patient as compared to treatment with MAD-S, which is not clinically relevant [41]. Although the freedom of vertical opening is different between MAD-H and MAD-S, it seems that the respiratory outcomes were not affected by this design feature. The same protrusion and vertical opening of the mandible in awake state may explain the similarity in treatment efficiency between MAD-H and MAD-S. However, as we did not measure the vertical opening in sleep, future studies are warranted to verify this hypothesis. Similar to our study, a retrospective study of Verburg et al. [21] also compared MAD-H and MAD-S and found no significant difference in improving the AHI. Thus, an MAD allowing limited vertical opening and an MAD allowing free vertical opening may result in similar respiratory outcomes.

No significant difference was found between both MADs in changing the upper airway dimensions. With the same protrusion position and vertical opening, the same effect of MAD-H and MAD-S was applied to the tongue and mandible in the awake state, and thus no difference of upper airway changes could be found between both groups. Our results are similar to the outcomes of two previous studies based on cephalometric images [16,42], in which no significantly different effects on the

upper airway dimensions were found when two MADs with similar protrusion and vertical opening were compared. However, limited to 2-D radiology images, those studies only compared the upper airway in anterior-posterior direction [16,42]. By using CBCT images, our study has the advantage of providing additional information on lateral direction dimension, CSAmin, and volume of the upper airway. The current CBCT scanning and measurement protocols were standardized, and have been proven to have an excellent reliability in the upper airway assessment in the present study (ICC = 0.90 to 0.96) as well as in our previous study [36]. However, a study of Ryan et al. [43] has suggested that different CBCT scanning timings of the same patient with same scanning and patient positioning protocols can result in different upper airway volumetric data, suggesting the intra-individual variability in CBCT assessments. However, this intra-individual variability was randomly present in both groups, and therefore may not explain our non-significant findings in the comparison between groups.

The self-reported side effects were not significantly different between both MAD groups. However, sensitive teeth and painful jaw muscles were 3-4 times more frequent in the MAD-H group compared to MAD-S group, which might be due to the different design feature. However, it seems that the side effects of MAD in most cases were of a minor nature and probably improve in the longer term [44,45]. A study with a long-term is needed to confirm the clinical relevance of our short-term finding.

4.2 Overall MAD effects

For respiratory parameters, there was a significant decrease in the AHI and AHI-non-supine but no significant decrease in the AHI-supine with MAD *in situ* in the total group, which indicated that the MADs used in this study were less effective in reducing the AHI in supine position. As MADs used in this study allow more or less freedom of vertical opening, gravity would favor mouth opening and weaken the beneficial effects of mandibular protrusion in supine position for both MADs. A study of Milano et al. [46] compared a group using an MAD allowing free vertical opening and a group using the same MAD with elastics to restrict the vertical opening, and suggested that the AHI-supine was improved significantly in both groups but that the improvement of AHI-supine was significantly greater in the group MAD with elastics. However, the patients in their study were positional OSA, which represents a different study sample as compared to our study and may explain the different effects of MAD allowing free vertical opening on AHI-supine. Inserting an MAD did not significantly change the time spent in supine position and REM stage, which is consistent with other studies [18, 47]. Given that sleeping in supine position and REM stage may worsen the respiratory events [48], the treatment effects of MAD in

the present study were not related to the time spent in supine position and/or REM stage at therapy evaluation.

The treatment response rate in the present study (48%) is in line with other studies reporting MAD response rate between 43% to 77% [49]. Using the same titration protocol and response rate criteria as the present study, the study of de Ruiter et al. [31] reported a 44.4% treatment response rate, which is in line with our results as well.

The CSAmin increased significantly with MAD *in situ* in the total group. Further, the increase of CSAmin was mainly due to the enlargement in the lateral dimension, which is similar to previous studies [50-52]. Although an MAD works primarily by protruding the mandible and tongue, the enlargement of the upper airway was predominantly in the lateral dimensions. The precise mechanism for this observation is not completely understood, but it has been suggested that this is related to the soft tissue connections between the tongue, soft palate, and lateral pharyngeal walls through the palatopharyngeal and palatoglossal arches [51]. Mandibular advancement possibly stretches the lateral pharyngeal walls through these soft tissue connections, and results in lateral enlargement of the CSAmin.

4.3 Limitations

The present study has several limitations. Firstly, the information of the patients who were initially screened for this study was missing. With these data missing, we cannot be certain that our sample represents the total population of OSA patients that are being seen in the clinics in Amsterdam. Although the dropout rate (36%) seemed high in our study, the dropout rate was comparable to our previous studies [33,53]. Importantly, there were no significant differences between dropouts and the participants in baseline characteristics. Further, the intention-to-treat analyses showed similar results as the per-protocol analyses. Secondly, the upper airway images were taken in awake state, and therefore the upper airway morphology may not be identical to the sleep state. Besides, CBCT assessment while awake does not reflect the actual effects of MAD on the upper airway in sleep as both types of MADs allow more or less mouth opening in sleep. However, it is currently challenging to scan the upper airway during sleep. To resemble the sleep state as much as possible, patients were instructed to relax their masticatory muscles with the MAD *in situ* when performing the follow-up CBCT scans. Importantly, since the CBCT scans at baseline and at therapy evaluation were both performed in awake supine condition, the effects of MADs on upper airway dimensions were unbiased. Thirdly, only a part of patients responded to the compliance telephone survey (response rate: 55%). It could be possible that patients who responded to the telephone survey in the

present study were more willing to use MAD, resulting in an overestimation of MAD compliance. Besides, the intensive follow-up titration protocol may also have contributed to a high compliance. Finally, subjective treatment outcomes, including snoring, daytime sleepiness (Epworth Sleepiness Scale), and quality of life, are also important therapeutic targets in patients with OSA, and therefore future studies should involve these aspects. Besides, as the present study investigated the treatment effect of both MADs in a short-term, a long-term follow-up study is needed to confirm our short-term findings.

4.4 Strengths

The standardized titration protocol used for both types of MAD is one of the major strengths of the present study. To the best of our knowledge, when comparing different MADs, few previous studies have reported a standardized titration protocol. In the present study, a detailed standardized titration protocol was applied, and no significant difference was found in finial protrusion position of both MAD groups, which enables an unbiased comparison. The standardized stepwise titration protocol for MAD, developed by one of the co-authors of this paper (GA), has been proved to have good efficacy, good tolerance, and good adherence [31], and is therefore recommended for use in clinical studies and practices.

Inserting an MAD intra-orally induces a certain amount of mandibular vertical opening. A study of Mayoral et al. [54] has indicated that as the vertical dimension increases, the mandible rotates posteriorly and places itself in a more retrusive location (0.3 mm for every 1 mm of vertical increase). Therefore, it is recommended to limit the vertical opening of MADs [54,55]. In this study, the vertical opening for MAD-H and for MAD-S in awake state were similar. To guarantee an accurate measurement of the vertical opening, we added the overbite and inter-incisor distance with MAD *in situ* together. As most previous studies only used inter-incisor distance to estimate the vertical opening, the accurate measurement of the vertical opening is another strength of the present study.

5. Conclusions

Within the limitations of this study, we conclude that there is no significant difference between the effects of an MAD allowing limited vertical opening and an MAD allowing free vertical opening on respiratory parameters and upper airway dimensions in patients with mild to moderate OSA.

Acknowledgments
The authors gratefully acknowledge Dr. Naichuan Su, department of oral public health, ACTA, for his assistance with the statistical analyses of this study; and the staff of the OLVG, Netherlands Slaap Instituut, Medisch Centrum Jan van Goyen and AMC for their assistance with this work.

Funding
Xiaoxin Shi has received a scholarship from the China Scholarship Council.

Disclosure of potential conflicts of interest
Xiaoxin Shi declares that she has no conflicts of interest. **Frank Lobbezoo** is a member of the Academic Advisory Boards for GrindCare and Oral Function of Sunstar Suisse S.A. and receives research grants from Sunstar Suisse S.A., SomnoMed, Vivisol, Health Holland, and Airway Management. **Hui Chen** declares that she has no conflicts of interest. **Boudewijn R.A.M. Rosenmöller** declares that he has no conflicts of interest. **Erwin Berkhout** declares that he has no conflicts of interest. **Jan de Lange** declares that he has no conflicts of interest. **Ghizlane Aarab** is a member of the Academic Advisory Board for Oral Function of Sunstar Suisse S.A. and receives research grants from Sunstar Suisse S.A., SomnoMed, Vivisol, and Health Holland.

References

1. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. (1999). Sleep 22 (5):667-689
2. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S (1993) The occurrence of sleep-disordered breathing among middle-aged adults. New England Journal of Medicine 328 (17):1230-1235
3. Gottlieb DJ, Whitney CW, Bonekat WH, Iber C, James GD, Lebowitz M, Nieto FJ, Rosenberg CE (1999) Relation of sleepiness to respiratory disturbance index: the Sleep Heart Health Study. American journal of respiratory and critical care medicine 159 (2):502-507
4. Peppard PE, Young T, Palta M, Skatrud J (2000) Prospective study of the association between sleep-disordered breathing and hypertension. New England Journal of Medicine 342 (19):1378-1384
5. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V (2005) Obstructive sleep apnea as a risk factor for stroke and death. New England Journal of Medicine 353 (19):2034-2041
6. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM (2010) Obstructive sleep apnea–hypopnea and incident stroke: the sleep heart health study. American journal of respiratory and critical care medicine 182 (2):269-277
7. Kendzerska T, Gershon AS, Hawker G, Tomlinson G, Leung RS (2014) Obstructive sleep apnea and incident diabetes. A historical cohort study. American journal of respiratory and critical care medicine 190 (2):218-225
8. Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ (2006) Continuous positive airways pressure for obstructive sleep apnoea in adults. The Cochrane database of systematic reviews (3):Cd001106. doi:10.1002/14651858.CD001106.pub3
9. Richard W, Venker J, den Herder C, Kox D, van den Berg B, Laman M, van Tinteren H, de Vries N (2007) Acceptance and long-term compliance of nCPAP in obstructive sleep apnea. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 264 (9):1081-1086. doi:10.1007/s00405-007-0311-3
10. Sharples LD, Clutterbuck-James AL, Glover MJ, Bennett MS, Chadwick R, Pittman MA, Quinnell TG (2016) Meta-analysis of randomised controlled trials of oral mandibular advancement devices and continuous positive airway pressure for obstructive sleep apnoea-hypopnoea. Sleep Med Rev 27:108-124. doi:10.1016/j.smrv.2015.05.003
11. Epstein LJ, Kristo D, Strollo PJ, Jr., Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM, Weinstein MD (2009) Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 5 (3):263-276
12. Randerath W, Verbraecken J, de Raaff CAL, Hedner J, Herkenrath S, Hohenhorst W, Jakob T, Marrone O, Marklund M, McNicholas WT, Morgan RL, Pepin JL, Schiza S, Skoetz N, Smyth D, Steier J, Tonia T, Trzepizur W, van Mechelen PH, Wijkstra P (2021) European Respiratory Society guideline on non-CPAP therapies for obstructive sleep apnoea. European respiratory review : an official journal of the European Respiratory Society 30 (162). doi:10.1183/16000617.0200-2021
13. Ahrens A, McGrath C, Hagg U (2011) A systematic review of the efficacy of oral appliance design in the management of obstructive sleep apnoea. European journal of orthodontics 33 (3):318-324. doi:10.1093/ejo/cjq079
14. Alsufyani NA, Al-Saleh MA, Major PW (2013) CBCT assessment of upper airway changes and treatment outcomes of obstructive sleep apnoea: a systematic review. Sleep and Breathing 17 (3):911-923
15. Ghazal A, Sorichter S, Jonas I, Rose EC (2009) A randomized prospective long-term study of two oral appliances for sleep apnoea treatment. Journal of sleep research 18 (3):321-328
16. Zhou J, Liu YH (2012) A randomised titrated crossover study comparing two oral appliances in the treatment for mild to moderate obstructive sleep apnoea/hypopnoea syndrome. J Oral Rehabil 39 (12):914-922. doi:10.1111/joor.12006
17. Umemoto G, Toyoshima H, Yamaguchi Y, Aoyagi N, Yoshimura C, Funakoshi K (2019) Therapeutic Efficacy of Twin-Block and Fixed Oral Appliances in Patients with Obstructive Sleep Apnea Syndrome. Journal of Prosthodontics 28 (2):e830-e836
18. Bloch KE, Iseli A, ZHANG JN, XIE X, KAPLAN V, STOECKLI PW, RUSSI EW (2000) A randomized, controlled crossover trial of two oral appliances for sleep apnea treatment. American journal of respiratory and critical care medicine 162 (1):246-251
19. Lee WH, Wee JH, Lee CH, Kim M-S, Rhee C-S, Yun P-Y, Yoon I-Y, Kim J-W (2013) Comparison between mono-bloc and bi-bloc mandibular advancement devices for obstructive sleep apnea. European Archives of Oto-Rhino-Laryngology 270 (11):2909-2913
20. Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, Chervin RD (2015) Clinical practice

guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015: an American Academy of Sleep Medicine and American Academy of Dental Sleep Medicine clinical practice guideline. Journal of clinical sleep medicine 11 (7):773-827
21. Verburg FE, Bollen KHA, Donker H-J, Kramer GJC (2018) The effectiveness of two types of MADS for OSA therapy. Clinical oral investigations 22 (5):1995-2003
22. Yoshida K (1998) Effect of a prosthetic appliance for treatment of sleep apnea syndrome on masticatory and tongue muscle activity. The Journal of prosthetic dentistry 79 (5):537-544
23. Ng AT, Gotsopoulos H, Qian J, Cistulli PA (2003) Effect of oral appliance therapy on upper airway collapsibility in obstructive sleep apnea. American journal of respiratory and critical care medicine 168 (2):238-241. doi:10.1164/rccm.200211-1275OC
24. Tsuiki S, Lowe AA, Almeida FR, Kawahata N, Fleetham JA (2004) Effects of mandibular advancement on airway curvature and obstructive sleep apnoea severity. The European respiratory journal 23 (2):263-268
25. Kim EJ, Choi JH, Kim KW, Kim TH, Lee SH, Lee HM, Shin C, Lee KY, Lee SH (2011) The impacts of open-mouth breathing on upper airway space in obstructive sleep apnea: 3-D MDCT analysis. European archives of oto-rhino-laryngology 268 (4):533-539
26. Vroegop AV, Vanderveken OM, Van de Heyning PH, Braem MJ (2012) Effects of vertical opening on pharyngeal dimensions in patients with obstructive sleep apnoea. Sleep medicine 13 (3):314-316
27. Barbero M, Flores-Mir C, Blanco JC, Nuño VC, Casellas JB, Girado JLC, Amezaga JA, De Carlos F (2020) Tridimensional upper airway assessment in male patients with OSA using oral advancement devices modifying their vertical dimension. Journal of Clinical Sleep Medicine 16 (10):1721-1729
28. Chen H, Aarab G, de Ruiter MH, de Lange J, Lobbezoo F, van der Stelt PF (2016) Three-dimensional imaging of the upper airway anatomy in obstructive sleep apnea: a systematic review. Sleep medicine 21:19-27. doi:10.1016/j.sleep.2016.01.022
29. Meurice J-C, Marc I, Carrier G, Sériès F (1996) Effects of mouth opening on upper airway collapsibility in normal sleeping subjects. American journal of respiratory and critical care medicine 153 (1):255-259
30. Isono S, Tanaka A, Tagaito Y, Ishikawa T, Nishino T (2004) Influences of head positions and bite opening on collapsibility of the passive pharynx. Journal of Applied Physiology 97 (1):339-346
31. De Ruiter M, Aarab G, De Vries N, Lobbezoo F, de Lange J (2020) A stepwise titration protocol for oral appliance therapy in positional obstructive sleep apnea patients: proof of concept. Sleep and Breathing 24 (3):1229-1236
32. Benoist LBL, Verhagen M, Torensma B, van Maanen JP, de Vries N (2017) Positional therapy in patients with residual positional obstructive sleep apnea after upper airway surgery. Sleep and Breathing 21 (2):279-288. doi:10.1007/s11325-016-1397-x
33. de Ruiter MHT, Benoist LBL, de Vries N, de Lange J (2018) Durability of treatment effects of the Sleep Position Trainer versus oral appliance therapy in positional OSA: 12-month follow-up of a randomized controlled trial. Sleep and Breathing 22 (2):441-450. doi:10.1007/s11325-017-1568-4
34. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF (2012) Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events: deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. Journal of clinical sleep medicine 8 (5):597-619
35. Camañes-Gonzalvo S, Bellot-Arcís C, Marco-Pitarch R, Montiel-Company JM, García-Selva M, Agustín-Panadero R, Paredes-Gallardo V, Puertas-Cuesta FJ (2022) Comparison of the phenotypic characteristics between responders and non-responders to obstructive sleep apnea treatment using mandibular advancement devices in adult patients: Systematic review and meta-analysis. Sleep Medicine Reviews 64:101644. doi:https://doi.org/10.1016/j.smrv.2022.101644
36. Chen H, Aarab G, Parsa A, de Lange J, van der Stelt PF, Lobbezoo F (2016) Reliability of three-dimensional measurements of the upper airway on cone beam computed tomography images. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 122 (1):104-110
37. Cohen J (1988) Statistical power analysis for the behavioral sciences. 2nd edn. Routledge, New York. https:// doi. org/ 10. 4324/97802 03771 587
38. Koo TK, Li MY (2016) A guideline of selecting and reporting intraclass correlation coefficients for reliability research. Journal of chiropractic medicine 15 (2):155-163
39. Kim HY (2018) Statistical notes for clinical researchers: analysis of covariance (ANCOVA). Restor Dent Endod 43(4):e43. https://doi. org/ 10. 5395/ rde. 2018. 43. e43
40. Armstrong RA (2014) When to use the Bonferroni correction. Ophthalmic Physiol Opt 34(5):502–508. https:// doi. org/ 10. 1111/opo. 12131
41. Kalso E, Edwards J, McQuay HJ, Moore RA (2001) Five easy pieces on evidence-based medicine (3). European journal of pain (London, England) 5 (2):227-230. doi:10.1053/eujp.2001.0242
42. Geoghegan F, Ahrens A, McGrath C, Hagg U (2015) An evaluation of two different mandibular advancement devices on craniofacial characteristics and upper airway dimensions of Chinese adult obstructive sleep apnea patients. The Angle orthodontist 85 (6):962-968. doi:10.2319/040314-245.1

43. Ryan DPO, Bianchi J, Ignácio J, Wolford LM, Gonçalves JR (2019) Cone-beam computed tomography airway measurements: Can we trust them? American Journal of Orthodontics and Dentofacial Orthopedics 156 (1):53-60
44. Lawton H, Battagel J, Kotecha B (2005) A comparison of the Twin Block and Herbst mandibular advancement splints in the treatment of patients with obstructive sleep apnoea: a prospective study. The European Journal of Orthodontics 27 (1):82-90
45. Pantin CC, Hillman DR, Tennant M (1999) Dental side effects of an oral device to treat snoring and obstructive sleep apnea. Sleep 22 (2):237-240
46. Milano F, Mutinelli S, Sutherland K, Milioli G, Scaramuzzino G, Cortesi A, Siciliani G, Lombardo L, Cistulli P (2018) Influence of vertical mouth opening on oral appliance treatment outcome in positional obstructive sleep apnea. J Dent Sleep Med 5 (1):17-23
47. Dieltjens M, Vroegop AV, Verbruggen AE, Wouters K, Willemen M, De Backer WA, Verbraecken JA, Van de Heyning PH, Braem MJ, de Vries N (2015) A promising concept of combination therapy for positional obstructive sleep apnea. Sleep and Breathing 19 (2):637-644
48. Eiseman NA, Westover MB, Ellenbogen JM, Bianchi MT (2012) The impact of body posture and sleep stages on sleep apnea severity in adults. Journal of Clinical Sleep Medicine 8 (6):655-666
49. Dieltjens M, Vanderveken OM, Van de Heyning PH, Braem MJ (2012) Current opinions and clinical practice in the titration of oral appliances in the treatment of sleep-disordered breathing. Sleep medicine reviews 16 (2):177-185
50. Chan AS, Sutherland K, Schwab RJ, Zeng B, Petocz P, Lee RW, Darendeliler MA, Cistulli PA (2010) The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. Thorax 65 (8):726-732
51. Sutherland K, Deane SA, Chan AS, Schwab RJ, Ng AT, Darendeliler MA, Cistulli PA (2011) Comparative effects of two oral appliances on upper airway structure in obstructive sleep apnea. Sleep 34 (4):469-477
52. Ryan C, Love L, Peat D, Fleetham J, Lowe A (1999) Mandibular advancement oral appliance therapy for obstructive sleep apnoea: effect on awake calibre of the velopharynx. Thorax 54 (11):972-977
53. Benoist L, de Ruiter M, de Lange J, de Vries N (2017) A randomized, controlled trial of positional therapy versus oral appliance therapy for position-dependent sleep apnea. Sleep Medicine 34:109-117. doi:https://doi.org/10.1016/j.sleep.2017.01.024
54. Mayoral P, Lagravère M, Míguez-Contreras M, Garcia M (2019) Antero-posterior mandibular position at different vertical levels for mandibular advancing device design. BMC Oral Health 19 (1):1-8
55. Nikolopoulou M, Naeije M, Aarab G, Hamburger H, Visscher C, Lobbezoo F (2011) The effect of raising the bite without mandibular protrusion on obstructive sleep apnoea. Journal of Oral Rehabilitation 38 (9):643-647

Chapter 6

Effects of mandibular advancement devices on upper airway dimensions in obstructive sleep apnea: responders versus non-responders

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Published as: Shi, X., Lobbezoo, F., Chen, H., Rosenmöller, B. R. A. M., Berkhout, E., de Lange, J., & Aarab, G. (2023). Effects of mandibular advancement devices on upper airway dimensions in obstructive sleep apnea: responders versus non-responders. Clinical oral investigations, 27(9), 5649–5660. https://doi.org/10.1007/s00784-023-05186-w

Abstract

Study Objectives

To compare the effects of mandibular advancement device (MAD) therapy on upper airway dimensions between responders and non-responders with mild to moderate obstructive sleep apnea (OSA).

Methods

Thirty-one participants (21 men and 10 women) with a mean ± SD apnea-hypopnea index (AHI) of 16.6 ± 6.7 events/h, and aged 48.5 ± 13.9 years, were included in this study. Polysomnographic recordings and cone beam computed tomography (CBCT) scans in supine position were performed for every participant at baseline and at 3-month follow-up with their MAD *in situ*. Responders were defined as having ≥ 50% reduction in baseline AHI with a residual AHI < 10 events/h. The primary outcome variable was the minimal cross-sectional area of the upper airway (CSAmin).

Results

No significant differences were found between responders (n = 15) and non-responders (n = 16) in age, gender distribution, body mass index, and neck circumference (P = 0.06-0.93), nor in AHI and CSAmin (P = 0.40 and 0.65, respectively) at baseline. The changes of the CSAmin with MAD *in situ* in the responder group were not significantly different compared to those in the non-responder group (P = 0.06).

Conclusion

Within the limitations of this study, we conclude that the changes of the upper airway dimensions induced by MADs are not significantly different between responders and non-responders with mild to moderate OSA.

Keywords

Obstructive sleep apnea, Mandibular advancement device, Cone beam computed tomography, Treatment response, Upper airway dimensions

1. Introduction

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder characterized by recurrent complete (i.e., apnea) and partial (i.e., hypopnea) obstructions of the upper airway, often resulting in oxygen desaturations and arousals from sleep [1,2]. The diagnosis of OSA depends on either the presence of apnea-hypopnea index (AHI) ≥ 15 events/h, or an AHI ≥ 5 events/h accompanied by one or more of the symptoms such as excessive daytime sleepiness, fatigue, or impaired cognition [1,2]. Most OSA patients have an impaired upper airway anatomy, which is also the key target of most existing treatments, such as continuous positive airway pressure (CPAP), upper airway surgery, weight loss, positional therapy, and mandibular advancement device (MAD) therapy [3,4]. Compared to other treatment options, MADs are easy to use, non-invasive, less expensive, and have similar treatment effects as CPAP in mild to moderate cases [5,6]. However, the efficacy of MAD therapy is variable and unpredictable, with approximately 50% non-responders [7-9] when using the recommended success criterion (i.e., ≥ 50% reduction in AHI with post-treatment AHI < 10 events/h) [10]. At this moment, the mechanism underlying different responses is not fully understood [11]. Therefore, there is an ongoing interest in the underlying mechanism of inter-individual variability in treatment responses. This knowledge is important for selecting the best candidates for MAD therapy.

The rationale behind the efficacy of MADs is that advancement of the mandible and tongue improves upper airway patency during sleep by enlarging the upper airway and by decreasing upper airway collapsibility [12-16]. However, the changes of the upper airway dimensions with the same mandibular advancement may differ between individuals due to many factors, such as the mandible morphology [17] and the soft tissue structures around the upper airway [18]. Some cephalometric studies suggested that the improvement of the upper airway dimensions was only observed in responders [13,14,19]. However, the 2-D images used in those studies could only provide limited information about the actual 3-D upper airway structures and may have projection errors [20]. Based on 3-D imaging techniques, such as magnetic resonance imaging (MRI) and cone beam computed tomography (CBCT), the differences observed in the effects of MADs on upper airway dimensions between responders and non-responders are not consistent. A study of Chan et al. [21] indicated that the enlargement of the upper airway dimensions with MAD *in situ* is present in responders only. By contrast, other studies suggested that there is no significant difference in the changes of upper airway dimensions between both groups [22-24]. The different results could be explained by the different imaging techniques (MRI vs. CBCT), imaging posture (supine vs. upright), and

the upper airway variables used. Besides, some of these studies have compared both groups in a sub-group analysis, with shortcomings of either having potential confounding factors (e.g., different baseline OSA severity) and/or small sample size. Consequently, whether the different effects of MAD on upper airway dimensions is one of the underlying mechanisms explaining responder and non-responder status has not yet been fully determined. Therefore, more evidence is needed to better understand the difference in the effects of MADs on upper airway dimensions between both groups.

Since the primary working mechanism of MAD is to improve the upper airway dimensions, we hypothesized the following: (1) with MAD *in situ*, responders will show a larger improvement of upper airway dimensions compared to non-responders; and (2) the improvement of the upper airway dimensions is positively associated with the improvement in the AHI. Therefore, the primary aim of this study was to compare the effects of MAD therapy on the upper airway dimensions between responders and non-responders with mild to moderate OSA based on CBCT images in the supine position. The secondary aim was to investigate the correlations between the changes in upper airway dimensions and the changes in AHI in the total group.

2. Methods

2.1 Overview

This study was part of a randomized controlled trial, in which individuals diagnosed with mild to moderate OSA (5 ≤ AHI < 30 events/h) were recruited to compare the efficacy of two types of MADs [25]. This study was approved by the Medical Research Ethics Committee of the Academic Medical Center Amsterdam (AMC), the Netherlands (#: NL44085.018.13). The study was registered at clinicaltrials.gov (ClinicalTrials.gov identifier: NCT02724865). Written informed consent was obtained from all participants.

2.2 Participants

Eligible patients, diagnosed with OSA at one of four sleep centers in the Netherlands (Onze Lieve Vrouwe Gasthuis Ziekenhuis, Nederlands Slaap Instituut, Medisch Centrum Jan van Goyen, and AMC), were referred to the department of Oral and Maxillofacial Surgery of the AMC to participate in the present study. The inclusion criteria were as follows: (1) ≥18 years old; (2) ability to speak, read, and write Dutch; (3) ability to follow-up; (4) ability to use a computer with internet connection for online questionnaires; (5) diagnosis with symptomatic mild or moderate OSA (5≤ apnea-hypopnea index (AHI)<30 events/h) with at least two OSA symptoms (e.g.,

snoring, fragmented sleep, witnessed apneas, and/or excessive daytime sleepiness [26]); and 6. expected to maintain current lifestyle (e.g., sports, medicine, diet). The exclusion criteria were as follows: (1) untreated periodontal problems, dental pain, and/or a lack of retention possibilities for an MAD; (2) medication usage that could influence respiration or sleep; (3) evidence of respiratory/sleep disorders other than OSA (e.g., central sleep apnea syndrome); (4) systematic disorders based on medical history and examination (e.g., rheumatoid arthritis); (5) severe temporomandibular disorders based on a functional examination of the masticatory system; (6) coexistence of non-respiratory sleep disorders (e.g., insomnia, periodic limb movement disorder, or narcolepsy); (7) known medical history of mental retardation, memory disorders, or psychiatric disorders; (8) reversible morphological upper airway abnormalities (e.g., enlarged tonsils, deviated nasal septum, and/or inferior nasal turbinate hypertrophy); (9) inability to provide informed consent; (10) simultaneous use of other modalities to treat OSA; and/or (11) previous treatment with an MAD.

2.3 MADs

Two types of MAD were used in this study, namely, MAD-H (Herbst appliance; 4Dental labs, Amsterdam, the Netherlands)) and MAD-S (SomnoDent appliance; SomnoDent Flex, SomnoMed, Sydney, Australia). Both types of MAD were titratable, two-piece, custom-made MADs, and were randomly allocated to the participants [25].

The detailed titration protocol was described previously [27]. In short, both types of MAD were set at 60% of the maximal mandibular advancement at baseline, and titrated backwards or forwards based on a weighted compromise between subjective improvement and side-effects during a 3-month follow-up. No adjustments were made when the patient reported sufficient efficacy without side effects.

2.4 Side effects and compliance

Self-reported side effects were recorded at each clinical visit, including the following: (1) sensitive teeth in the morning; (2) painful jaw muscles; (3) painful temporomandibular joints; and (4) changed occlusion in the morning. Information about the adherence and satisfaction level was collected by a telephone survey, which were expressed as follows: (1) percentage of hours of MAD use per total sleep time, (2) percentage of days of MAD use per week, and (3) the overall level of satisfaction with the MAD usage.

2.5 Polysomnographic (PSG) recordings

This study consisted of two PSG recordings for each participant: one at baseline without MAD and one at 3-month follow-up with MAD *in situ*. A digital PSG system

(Embla A10, Broomfield, CO, USA) was used and recorded electroencephalogram (EEG) (FP2-C4/C4-O2), electrooculogram (EOG), electrocardiogram (ECG), and submental and anterior tibial electromyogram (EMG). Nasal airflow was measured by a nasal pressure cannula, and blood oxygen saturation was measured by finger pulse oximetry. Straps containing piezoelectric transducers recorded thoracoabdominal motion, and a position sensor (Sleepsense, St Charles, IL, USA) attached to the midline of the abdominal wall was used to differentiate between supine, prone, right lateral, left lateral, and upright positions [28,29].

PSG parameters, including sleep and respiratory variables, were analyzed following the recommendations of the American Academy of Sleep Medicine [1]. Responders were defined as having ≥ 50% reduction in baseline AHI with a residual AHI <10 events/h at the time of therapy evaluation. If this criterion was not met, patients were regarded as non-responders [10].

2.6 CBCT scans

Two CBCT scans (NewTom 5G, QR systems, Italy) were performed for every participant at the department of Oral Radiology of the Academic Centre for Dentistry Amsterdam (ACTA): one without MAD at baseline and one with MAD *in situ* at 3-month follow-up in the same protrusion position as during the follow-up PSG recording. CBCT scans were performed while the patient was awake in the supine position with quiet breathing. The head of the patient was positioned with the Frankfort plane being perpendicular to the floor. After CBCT scanning, we further standardized the head position, during which the palatal plane (anterior nasal spine (ANS)-posterior nasal spine (PNS)) was adjusted to be parallel to the axial plane and the sagittal plane, and perpendicular to the coronal plane [30]. CBCT datasets were saved as Digital Imaging and Communications in Medicine (DICOM) files for further analysis.

2.7 Craniofacial characteristics

Measurements of the positions of the maxilla and mandible were performed using 3Diagnosys® software (v5.3.1, 3diemme, Cantu, Italy). The angle between sella, nasion, and subspinale (SNA angle), and the angle between sella, nasion, and supramentale (SNB angle) were used to represent the anteroposterior position of the maxilla and mandible relative to the cranial base, respectively. Landmarks are illustrated in **Fig. 1A**.

2.8 Upper airway dimensions

The measurements of upper airway dimensions were performed using the Amira® software (v4.1, Visage Imaging Inc., Carlsbad, CA, USA). After setting the superior

boundary of the upper airway (i.e., the palatal plane) and the inferior boundary (i.e., the horizontal plane across the base of the epiglottis) (**Fig. 1A**), the volume of the upper airway (V), the sequence number of each slice, and the cross-sectional area (CSA) of each slice were calculated automatically in the software [30]. Based on the CSA, the minimum CSA (CSAmin) could be identified and located (**Fig. 1B**), on which the anteroposterior dimension (A-P) and lateral dimension (La) of CSAmin could be measured (**Fig. 1C**). Based on the slice numbers of the upper airway, the length of upper airway (L) was calculated by multiplying the slice number with 0.3mm (the thickness of every slice). The investigator was blinded for the treatment response.

Since the CSAmin is suggested to be the most relevant anatomical characteristic related to the pathogenesis of OSA [31], the CSAmin was the primary outcome variable of the upper airway dimensions. The secondary upper airway variables included the lateral dimension (La) and anteroposterior dimension (A-P) of the CSAmin, upper airway volume (V), and upper airway length (L).

An experienced examiner who was blinded to the membership of the patients measured all the upper airway variables. Ten CBCT scans were randomly selected and re-measured after a 1-month interval of the original measurements, and the intra-rater reliability was assessed.

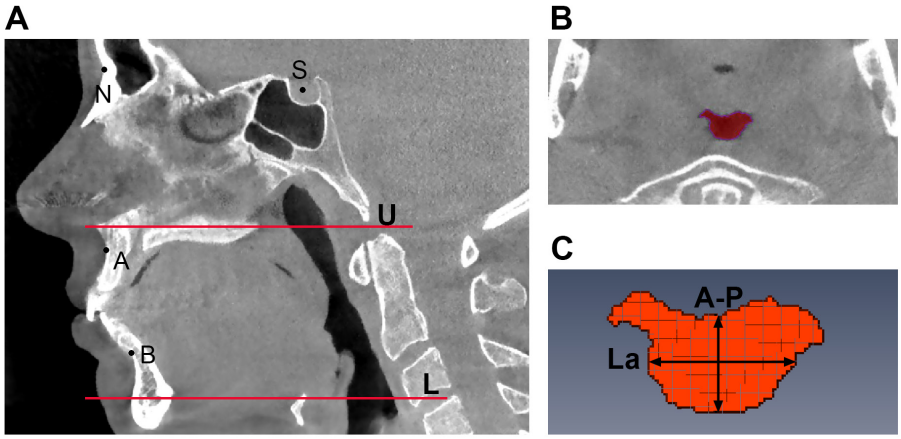

Fig. 1 Craniofacial landmarks and measurements of the upper airway dimensions based on cone beam computed tomography (CBCT) imaging. **A.** N = nasion, S = sella, A = subspinale, B = supramentale, U= the upper boundary of the upper airway (hard palate plane), L = the lower boundary of the upper airway (plane cross the base of the epiglottis) on the mid-sagittal plane. **B.** The minimal cross-sectional area of the upper airway (CSAmin) on the axial plane. **C**. The measurement of the anterior-posterior dimension (A-P) and the lateral dimension (La) of the CSAmin

2.9 Statistical analysis

Normality assumptions were verified with the Shapiro–Wilk test. Independent *t* test (for normally distributed variables), Mann-Whitney *U* test (for non-normally distributed variables), and Chi-squared test or Fisher's exact test (for categorical variables) were used to compare the baseline demographic and craniofacial characteristics, as well as MAD type, mandibular protrusion, side effects, and adherence reports between the responder group and the non-responder group.

A two-way mixed, absolute agreement, single measures intraclass correlation coefficient (ICC) was used to determine the intra-rater reliability for the upper airway variables. Analyses of covariance (ANCOVA) were used to compare changes in sleep, respiratory, and upper airway variables between baseline and therapy evaluation between both groups. Significantly different baseline characteristics between responders and non-responders were controlled for as covariates [32]. Bonferroni-Holm method was used to correct the multiple comparisons of the secondary outcome variables of the upper airway [33]. Correlations between the changes in respiratory variables and the changes in upper airway dimensions were assessed using Pearson's correlations (for normally distributed variables) or Spearman's correlation (for non-normally distributed variables).

To test the robustness of the results of ANCOVA and correlation analyses, sensitivity analyses were performed by excluding the outliers of the primary variable (i.e., CSAmin) [34]. An outlier was defined as individual patients with the change of the primary variable (i.e., the change of CSAmin) more than 3 times the interquartile range (IQR) of the change above the 75th percentile or below the 25th percentile of all participants.

Statistical analysis was performed using the SPSS software (SPSS version 26, Chicago, IL, USA). A post-hoc power analysis was conducted for the primary outcome variable (i.e., CSAmin) using software G*power (version 3.1.9, Franz Faul, Universität Kiel, Germany).

3. Results

3.1 Recruitment

Of the 49 patients who were initially recruited, 18 patients were excluded for reasons of lost contact (n = 5), quit study due to MAD complaints (n = 4), refused the second PSG recordings (n = 2), and with incomplete dataset (n = 7). Finally, 31 patients were included in this study: 15 of them were classified as responders, and

16 were non-responders.

3.2 Patient characteristics

The baseline demographic and craniofacial characteristics of the responder group and the non-responder group are shown in **Table 1**. There were no significant differences between responders (n = 15) and non-responders (n = 16) in gender distribution, body mass index (BMI), neck circumference, and OSA severity categories (P = 0.61-0.93). Besides, there were no significant differences in SNA angle and SNB angle between both groups (P = 0.50 and 0.34, respectively). The responder group (43.7 ± 11.1 years) tended to be significantly younger than the non-responder group (52.9 ± 15.1 years) (t = -1.93, P = 0.06). Therefore, age was considered a covariate in the ANCOVA.

Table 1 Baseline demographic and craniofacial characteristics of the responder group and the non-responder group

	Responders (n = 15)	**Non-responders (n = 16)**	**Test statistics**	***P***
Demographic characteristics				
Age (years)	43.7 ± 11.1	52.9 ± 15.1	-1.93 (t)	0.06
Gender (men vs. women)	11 vs. 4	10 vs. 6	FET	0.70
BMI (kg/m^2)	25.0|26.0|29.4	24.0|27.4|30.7	-0.38 (Z)	0.71
Neck circumference (cm)	38.9 ± 4.0	39.1 ± 4.0	-0.09 (t)	0.93
OSA severity (mild vs. moderate)	6 vs. 9	5 vs. 11	0.26 (χ^2)	0.61
Craniofacial characteristics				
SNA (°)	78.3|81.5|84.7	79.6|80.8|84.8	-0.67 (Z)	0.50
SNB (°)	76.7 ± 4.3	78.1 ± 3.8	-0.96 (t)	0.34

Normally distributed data are shown as mean ± standard deviation (SD); non-normally distributed data are presented as 25th percentile|median|75th percentile; *t,* independent t test; *Z,* Mann-Whitney U test; *FET,* Fisher's exact test; χ^2, Chi-squared test; *BMI,* body mass index, *mild OSA severity,* 5 ≤ AHI < 15 events/h; *moderate OSA severity,* 15 ≤ AHI < 30 events/h; *SNA,* angle between sella, nasion, and subspinale; *SNB,* angle between sella, nasion, and supramentale

3.3 MAD use

The MAD type, amount of mandibular advancement, side effects, and adherence reports of the responder group and the non-responder group are presented in **Table 2**. There was no significant difference in MAD type used between both groups (χ^2 = 0.03, P = 0.85). Besides, no significant difference was found between both groups in the amount of mandible advancement in both percentage (%) and actual amount (mm) of the maximum protrusion (P = 0.34 and 0.12, respectively). No significant difference was found between both groups in their side effects either (P = 0.33-0.65). Nine patients in the responder group and 8 patients in the non-responder

group responded on the adherence questionnaire. No significant differences in adherence reports were found between both groups (P = 0.29-0.86).

Table 2 MAD type, amount of mandibular advancement, side effects, and adherence reports of the responder group and the non-responder group

	Responders (n = 15)	**Non-responders (n = 16)**	***t/Z/χ²/FET***	***P***
MAD type				
MAD-H vs. MAD-S	8 vs. 7	8 vs. 8	0.03 (χ^2)	0.85
Mandibular advancement				
Advancement (%)	70.0|75.0|90.0	62.5|75.0|75.0	-0.96 (Z)	0.34
Advancement (mm)	9.2 ± 2.5	8.0 ± 1.6	1.60 (t)	0.12
Side effects				
Sensitive teeth in the morning	3	2	FET	0.65
Painful jaw muscles	1	3	FET	0.60
Painful temporomandibular joints	4	2	FET	0.39
Changed occlusion in the morning	1	4	FET	0.33
Adherence	*(n = 9)* [a]	*(n = 8)* [a]		
Wearing hour (%)	100.0|100.0|100.0	100.0|100.0|100.0	-0.17 (Z)	0.86
Wearing day (%)	100.0|100.0|100.0	100.0|100.0|100.0	-1.06 (Z)	0.29
Level of satisfaction (%)	68.9 ± 25.1	76.0 ± 16.1	-0.69 (t)	0.50

Normally distributed data are shown as mean ± standard deviation (SD); non-normally distributed data are presented as 25th percentile|median|75th percentile; *t,* independent t test; *Z,* Mann-Whitney U test; *χ^2,* Chi-squared test; *FET,* Fisher's exact test; [a], compliance data were available for 9 patients of responder group and 8 patients of non-responder group
MAD, mandibular advancement device; *MAD-H,* MAD of Herbst type; *MAD-S,* MAD of SomnoDent type

3.4 Reliability of the upper airway assessment

The intra-rater reliability for the upper airway assessment was excellent, with ICC = 0.96 for the CSAmin and ICC = 0.90 to 0.94 for the secondary outcome variables [35].

3.5 Sleep and respiratory variables

The sleep and respiratory variables at baseline and at 3-month follow-up with MAD *in situ* of the responder and non-responder groups are shown in **Table 3**. The baseline values of the sleep and respiratory variables were not significantly different between both groups (P = 0.10-0.97). By definition, the reductions of AHI and AHI-supine were significantly larger in responders compared to non-responders (P < 0.01 and < 0.01, respectively). However, the changes of AHI-non-supine, oxygen desaturation index (ODI), and sleep variables were not significantly different between both groups (P = 0.16-0.93).

Table 3 Sleep and respiratory variables at baseline and at 3-month follow-up of the responder group and the non-responder group

	responders (*n* = 15)		non-responders (*n* = 16)		Baseline comparisons (ANCOVA)		Therapy effects comparisons (ANCOVA)	
	Baseline	3-month	Baseline	3-month	*F*	*P*	*F*	*P*
Sleep variables [a]								
Total sleep time (min)	398.3 ± 53.9	416.7 ± 47.8	408.1 ± 75.0	406.2 ± 78.8	0.97	0.33	1.38	0.25
Stage N1 (%)	7.4 ± 5.2	6.0 ± 4.5	10.3 ± 4.7	8.3 ± 6.7	1.92	0.18	0.29	0.60
Stage N2 (%)	54.2 ± 7.5	49.9 ± 11.7	49.7 ± 9.3	45.9 ± 11.3	2.98	0.10	0.05	0.83
Stage N3 (%)	17.3 ± 7.4	19.7 ± 8.6	19.4 ± 5.8	23.5 ± 8.5	1.34	0.26	0.23	0.63
Stage REM (%)	21.1 ± 4.5	24.3 ± 5.8	20.6 ± 6.0	22.3 ± 7.4	0.00	0.97	0.21	0.65
Supine position (%)	44.4 ± 37.4	37.1 ± 27.3	39.9 ± 27.0	42.3 ± 27.6	0.00	0.97	0.76	0.39
Arousal index(/h)	7.9 ± 5.3	11.5 ± 11.8	11.8 ± 16.0	14.2 ± 13.5	0.87	0.36	0.01	0.93
Respiratory variables								
AHI (/h)	15.9 ± 6.1	4.9 ± 2.6	17.3 ± 7.3	17.1 ± 6.8	0.72	0.40	15.38	<0.01*
AHI-supine (/h)	29.8 ± 16.1	9.9 ± 10.9	30.4 ± 15.4	34.3 ± 22.5	0.00	0.97	10.76	<0.01*
AHI-non-supine (/h)	8.3 ± 8.2	3.2 ± 2.7	11.0 ± 8.5	7.1 ± 4.0	0.57	0.46	0.16	0.69
ODI (/h)	16.0 ± 8.9	8.0 ± 4.4	16.1 ± 11.3	15.0 ± 7.5	0.39	0.54	2.12	0.16

Data are shown as mean ± standard deviation (SD); *ANCOVA*, analysis of covariance using age as a covariate; [a], two patients with incomplete sleep data were excluded from the analysis of sleep variables; * statistically significant

REM, rapid-eye-movement; *AHI,* apnea-hypopnea index; *AHI-supine,* AHI score in the supine position; *AHI-non-supine,* AHI score in positions other than the supine position; *ODI*, oxygen desaturation index

3.6 Upper airway variables

The variables of upper airway dimensions at baseline and at 3-month follow-up with MAD *in situ* in the responder group and the non-responder group are presented in **Table 4**. For the primary outcome variable, CSAmin, the enlargement of CSAmin with MAD *in situ* was not significantly different between both groups (P = 0.06). The individual values of the CSAmin at baseline and at follow-up in the responder and non-responder groups are illustrated in **Fig. 2**. For the secondary upper airway variables, there were no significant differences between both groups in the changes of A-P dimensions, La dimensions, upper airway volume, and upper airway length after Bonferroni-Holm correction (P = 0.04-0.18). Similar results were found in the sensitivity analyses of ANCOVA after excluding the two outliers in the non-responder group: there were no significant differences between both groups in the changes of the CSAmin (P = 0.20) and the secondary outcome variables (P = 0.11-0.54) either. The observed effect size f of the changes of CSAmin between both groups was 0.37 in the primary analysis (partial η^2 = 0.12, ANCOVA) and 0.25 in the sensitivity analysis (partial η^2 = 0.06, ANCOVA), which can be qualified as between medium and large.

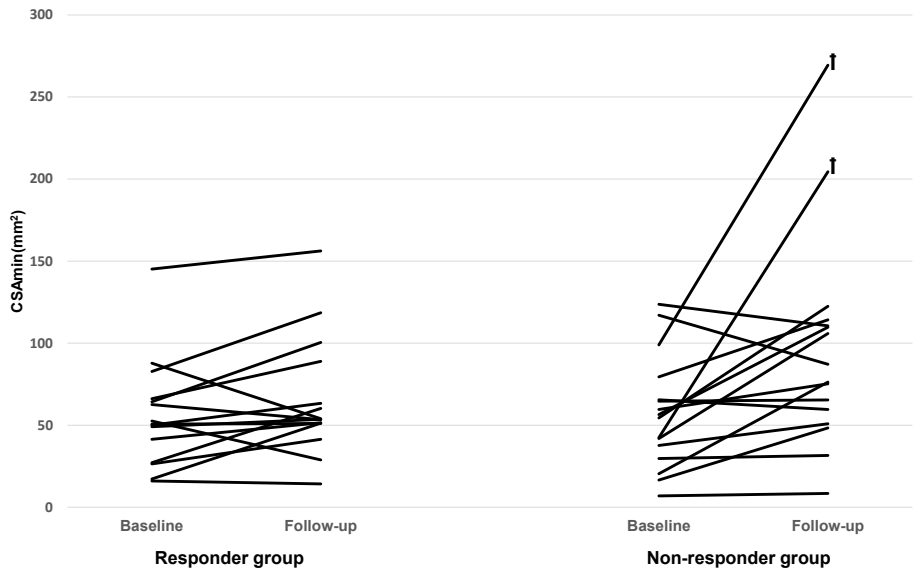

Fig. 2 Individual values of the minimal cross-sectional area of the upper airway (CSAmin) at baseline and at follow-up in the responder group (n = 15) and the non-responder group (n = 16). No significant difference was observed in the changes in the CSAmin between both groups (P = 0.06). ↑: outliers

Table 4 Variables of upper airway dimensions at baseline and at 3-month follow-up with MAD *in situ* of the responder and non-responder groups

	Responders (*n* = 15)		**Non-responders (*n* = 16)**		**Baseline comparisons (ANCOVA)**		**Therapy effects comparisons (ANCOVA)**	
	Baseline	3-month	Baseline	3-month	*F*	*P*	*F*	*P*
Primary outcome								
CSAmin (mm^2)	55.9 ± 32.8	65.8 ± 36.3	57.2 ± 34.1	96.2 ± 64.6	0.22	0.65	3.80	0.06
Secondary outcomes								
A-P (mm)	4.8 ± 1.8	4.9 ± 1.5	4.3 ± 1.9	5.4 ± 2.6	1.32	0.26	1.89	0.18
La (mm)	12.1 ± 3.6	14.3 ± 4.3	12.3 ± 5.6	17.1 ± 6.0	0.02	0.89	3.61	0.07
V (cm^3)	9.5 ± 2.9	10.0 ± 3.6	12.6 ± 5.1	14.9 ± 6.0	1.92	0.18	2.60	0.12
L (mm)	65.3 ± 9.5	62.4 ± 9.5	67.5 ± 8.1	67.4 ± 8.7	0.26	0.61	4.90	0.04

Data are shown as mean ± standard deviation (SD); *ANCOVA,* analysis of covariance using age as a covariate; *CSAmin,* minimum cross-sectional area of the upper airway; *A-P,* anteroposterior dimension of the CSAmin; *La,* lateral dimension of the CSAmin; *V,* volume of the upper airway; *L,* length of the upper airway

3.7 Correlations

The correlations between the changes in upper airway dimensions and the changes in the respiratory variables of the total group are shown in **Table 5**. There were no significant correlations between the changes in CSAmin and the changes in AHI (P = 0.48), AHI-supine (P = 0.10), and AHI-non-supine (P = 0.59). Besides, no significant correlations were found between the changes in the secondary upper airway variables and the changes in the respiratory variables either (all $P > 0.05$). Similar results were found in the sensitivity analyses of correlation analyses after excluding the two outliers in the non-responder group: no significant correlations were found between the changes in upper airway dimensions and the changes in the respiratory variables (all $P > 0.05$).

Table 5 Correlations between the changes in upper airway dimensions and the changes in the respiratory variables of all participants with OSA (n = 31)

	ΔAHI		**ΔAHI-supine**		**ΔAHI-non-supine**	
	r	*P*	*r*	*P*	*r*	*P*
ΔCSAmin (mm^2)	0.13	0.48	0.30	0.10	-0.10	0.59
ΔA-P (mm)	0.05	0.81	0.09	0.63	-0.21	0.27
ΔLa (mm)	0.18	0.32	0.27	0.15	0.07	0.73
ΔV (cm^3)	0.26	0.15	0.25	0.18	-0.27	0.15
ΔL (mm)	0.30	0.10	0.13	0.48	0.02	0.90

Δ, the difference between the baseline value and follow-up value; *r*, correlation coefficient; *CSAmin*, minimum cross-sectional area of the upper airway; *A-P*, anteroposterior dimension of the CSAmin; *La,* lateral dimension of the CSAmin; *V*, volume of the upper airway; *L*, length of the upper airway; *AHI*, apnea-hypopnea index; *AHI-supine,* AHI scores in the supine position; *AHI-non-supine,* AHI scores in positions other than the supine position

4. Discussion

The objectives of this study were to compare the effects of MAD therapy on upper airway dimensions between responders and non-responders with mild to moderate OSA, and to determine the correlations between the changes in upper airway dimensions and the changes in AHI in the total group. The results indicated that the changes of the upper airway dimensions with MAD *in situ* were not significantly different between responders and non-responders in the supine position. Furthermore, the changes of the upper airway dimensions had no significant correlation with the changes in AHI.

4.1 Comparisons of the therapy effects on upper airway dimensions

The changes of CSAmin induced by MAD were not significantly different between responders and non-responders in the present study. Besides the CSAmin,

the secondary outcome variables, including the lateral dimensions and the anteroposterior dimensions of the CSAmin, upper airway volume, and upper airway length, were not significantly different between both groups either. Contrary to our results, Chan et al. [21] compared 47 responders and 22 non-responders based on MRI and found a significant increase in the CSAmin and other upper airway dimensions in responders only. However, in their study, the responders had significantly higher AHI and bigger SNB angle compared to the non-responders at baseline, which may bias the upper airway comparisons and may explain the different results as compared to our findings. Our results are similar to three other studies [22-24], which all suggested that there were no significant differences between responders and non-responders regarding the changes of upper airway dimensions based on 3-D images. However, the generalization of these three studies might be limited due to different aspects. In the study of Pahkala et al. [24], the measurements of the upper airway dimensions were based on upright CBCT images, which may represent different upper airway dimensions compared to those based on supine images [36]. The study of Ogawa et al. [23] compared the upper airway dimensions based on the mid-sagittal plane of a MRI image only, and in the study of Sutherland et al. [22], the comparisons were performed as a sub-group analysis with a small sample (12 responders vs. 6 non-responders). Therefore, our study confirmed the results of previous studies with larger sample size and different upper airway variables in the supine position. The outcomes suggest that the enlargement of the upper airway with MAD *in situ* in the supine position during waking state cannot explain treatment success of MAD treatment.

In the present study, the observed effect size f of the difference in the changes of CSAmin between both groups (0.37 and 0.25 in the primary and sensitivity analyses, respectively) was between medium and large (according to Cohen [37], an effect size f = 0.10 is small, f = 0.25 is medium, and f = 0.40 is large). With these effect sizes, if we enlarge our sample size to around 60-130, there might be a significant difference between both groups (with power 0.8 and 5% significance level). However, it is important to note is that there is a tendency that non-responders will have a greater enlargement of CSAmin compared to responders, which confirms the aforementioned speculation that the upper airway enlargement by itself cannot explain treatment success.

Our results suggest that the effects of MAD on upper airway dimensions are similar between responders and non-responders in the supine position, although the changes of AHI and AHI-supine differed significantly. The non-significant findings of comparisons of upper airway dimensions do not support our initial hypothesis. However, the multifactorial nature of the pathogenesis of OSA may possibly

explain our findings. It has been recognized that besides anatomical factors, non-anatomical factors like impaired pharyngeal dilator muscle responsiveness, increased propensity for awakening during airway narrowing (low respiratory arousal threshold), and respiratory control instability (high loop gain) are also crucial determinants of OSA for many patients [4]. Therefore, we hypothesize that the mechanical enlargement of the upper airway dimensions is an important prerequisite for treatment success of MAD, but the finial treatment outcome may be mediated by non-anatomical factors. Limited by technique, the non-anatomical factors could not be investigated for responders and non-responders in the present study. However, previous studies have suggested that compared to non-responders, responders had a less collapsible pharynx and a more stable respiratory control system (i.e., lower loop gain) [38,39], which is in line with our hypothesis. Future studies are warranted to test this hypothesis.

4.2 Correlations

No significant correlations were found between the changes in upper airway dimensions and the changes in AHI. Furthermore, as the upper airway images were performed in the supine position, the correlations between the changes in upper airway dimensions and the changes in AHI-supine were also investigated, and no significant correlations were found either. Our results are consistent with other studies [14,22,40,41], in which no significant linear correlations were found between the changes in AHI and the changes in upper airway dimensions. In contrast, a study of Camañes-Gonzalvo et al. [16] has found a significant correlation between the increase of the upper airway volume and the decrease of AHI. However, the correlation was only significant in the severe OSA group, and not in the mild to moderate groups [16], which corresponds with the findings in the present study. Since OSA pathogenesis is explained by both anatomical and non-anatomical factors [4], it is to be expected that the relationship between the changes in respiratory parameters and the changes in the upper airway dimensions is not linear. The absence of a significant correlation is also in line with our non-significant finding in the comparisons of upper airway changes between both groups, which suggests that the prediction of treatment response of MAD using upper airway changes based on awake CBCT is of limited value.

4.3 Demographic characteristics

Many studies have hypothesized that some demographic and craniofacial characteristics could be helpful in predicting the treatment success of MAD therapy. In the present study, responders were younger than non-responders, which is consistent with previous studies [42-45]. According to a recent systematic review and meta-analysis study [10], other characteristics that may associate with MAD

treatment success are lower BMI, smaller neck circumference, a shorter airway length, and a smaller baseline CSAmin. However, the results of this study did not confirm these findings, which may be related to the size and/or heterogeneity of our sample in our study. In general, no single characteristic may reliably predict a favorable MAD treatment outcome [46], which calls for more research in the recognition of non-responders by combining demographic characteristics, anatomical factors, and non-anatomical factors.

4.4 Vertical opening

The MADs used in the present study are customized adjustable devices which allow some degree of mouth opening during sleep [25]. When using similar customized adjustable devices (allowing mouth opening) and the same success criterion, the treatment success rate of the present study (48%) is consistent with previous studies reporting a success rate of approximately 50% [7,8,38]. However, studies have shown that increased mouth opening during sleep may compromise the beneficial effects of MAD therapy on upper airway dimensions and the treatment efficacy [47,48]. It has been suggested that using elastic bands restricting the mouth opening during sleep may help improve the treatment efficacy of these MADs [49,50]. In the pilot study of Norrhem et al. [49], MADs with elastic bands markedly reduced the supine AHI in 2 severe OSA patients, however, there was no significant difference in the overall AHI reduction between MADs with or without elastic bands. In the study of Milano et al. [50], the treatment efficacy was significantly higher in the MADs with elastic bands than the MADs without elastic bands in positional OSA patients, which may not represent the general OSA population. Therefore, well designed RCTs are needed to investigate whether restricting the mouth opening increases the efficacy of the MADs that allow mouth opening.

4.5 Study limitations

The present study has several limitations. First, the CBCT scans were performed in awake state. Therefore, the upper airway morphology may not be the same as that in sleep state. However, acquiring a radiologic image of the upper airway during sleep is clinically challenging. Besides, as the baseline and follow-up CBCT images in our study were both taken in the supine position, the comparisons of the changes of upper airway between responders and non-responders were not biased. Second, two types of MAD were used in this study. However, our previous study has suggested that there was no significant difference between these two types of MAD in affecting PSG parameters and upper airway dimensions [25]. Furthermore, in both groups, similar numbers of both MAD types were used. Therefore, we believe only limited bias was caused by including these two types of MAD in our study. In addition, as this study recruited patients in an RCT study with another primary

aim [25], we did not perform an *a priori* power analysis to calculate the sample size. The effect size analyses of the primary outcome variable indicated that with a larger sample size (n = 60-130 based on the primary and sensitivity analyses), non-responders tend to have a greater enlargement of CSAmin compared to responders.

5. Conclusion

Within the limitations of this study, we conclude that the changes of the upper airway dimensions induced by MADs are not significantly different between responders and non-responders with mild to moderate OSA. Furthermore, the changes of the upper airway dimensions have no significant correlations with the changes in the apnea-hypopnea index.

Acknowledgement
We gratefully acknowledge the statistical advice of Dr. Naichuan Su, department of Oral Public Health, Academic Centre for Dentistry Amsterdam (ACTA).

Funding
Xiaoxin Shi has received a scholarship from the China Scholarship Council.

Conflicts of interests
Xiaoxin Shi declares that she has no conflicts of interest. **Frank Lobbezoo** is a member of the Academic Advisory Boards for GrindCare and Oral Function of Sunstar Suisse S.A. and receives research grants from Sunstar Suisse S.A., SomnoMed, Vivisol, Health Holland, and Airway Management. **Hui Chen** declares that she has no conflicts of interest. **Boudewijn R.A.M. Rosenmöller** declares that he has no conflicts of interest. **Erwin Berkhout** declares that he has no conflicts of interest. **Jan de Lange** declares that he has no conflicts of interest. **Ghizlane Aarab** is a member of the Academic Advisory Board for Oral Function of Sunstar Suisse S.A. and receives research grants from Sunstar Suisse S.A., SomnoMed, Vivisol, and Health Holland.

References

1. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF (2012) Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events: deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. Journal of clinical sleep medicine 8 (5):597-619
2. Berry RB, Brooks R, Gamaldo C, Harding SM, Lloyd RM, Quan SF, Troester MT, Vaughn BV (2017) AASM Scoring Manual Updates for 2017 (Version 2.4). Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 13 (5):665-666. Doi:10.5664/jcsm.6576
3. Carberry JC, Amatoury J, Eckert DJ (2018) Personalized management approach for OSA. Chest 153 (3):744-755
4. Eckert DJ (2018) Phenotypic approaches to obstructive sleep apnoea–new pathways for targeted therapy. Sleep medicine reviews 37:45-59
5. Aarab G, Lobbezoo F, Hamburger HL, Naeije M (2011) Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial. Respiration 81 (5):411-419
6. Randerath W, Verbraecken J, de Raaff CAL, Hedner J, Herkenrath S, Hohenhorst W, Jakob T, Marrone O, Marklund M, McNicholas WT, Morgan RL, Pepin JL, Schiza S, Skoetz N, Smyth D, Steier J, Tonia T, Trzepizur W, van Mechelen PH, Wijkstra P (2021) European Respiratory Society guideline on non-CPAP therapies for obstructive sleep apnoea. European respiratory review : an official journal of the European Respiratory Society 30 (162). Doi:10.1183/16000617.0200-2021
7. Sutherland K, Chan ASL, Ngiam J, Dalci O, Darendeliler MA, Cistulli PA (2018) Awake Multimodal Phenotyping for Prediction of Oral Appliance Treatment Outcome. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 14 (11):1879-1887. Doi:10.5664/jcsm.7484
8. Brown EC, Jugé L, Knapman FL, Burke PGR, Ngiam J, Sutherland K, Butler JE, Eckert DJ, Cistulli PA, Bilston LE (2021) Mandibular advancement splint response is associated with the pterygomandibular raphe. Sleep 44 (4). Doi:10.1093/sleep/zsaa222
9. Venema JAU, Rosenmöller BR, De Vries N, de Lange J, Aarab G, Lobbezoo F, Hoekema A (2021) Mandibular advancement device design: A systematic review on outcomes in obstructive sleep apnea treatment. Sleep medicine reviews 60:101557
10. Camañes-Gonzalvo S, Bellot-Arcís C, Marco-Pitarch R, Montiel-Company JM, García-Selva M, Agustín-Panadero R, Paredes-Gallardo V, Puertas-Cuesta FJ (2022) Comparison of the phenotypic characteristics between responders and non-responders to obstructive sleep apnea treatment using mandibular advancement devices in adult patients: Systematic review and meta-analysis. Sleep Medicine Reviews 64:101644. Doi:https://doi.org/10.1016/j.smrv.2022.101644
11. Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, Chervin RD (2015) Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 11 (7):773-827. Doi:10.5664/jcsm.4858
12. Chan A, Lee R, Srinivasan V, Darendeliler M, Grunstein R, Cistulli P (2010) Nasopharyngoscopic evaluation of oral appliance therapy for obstructive sleep apnoea. European Respiratory Journal 35 (4):836-842
13. Tsuiki S, Lowe AA, Almeida FR, Fleetham JA (2004) Effects of an anteriorly titrated mandibular position on awake airway and obstructive sleep apnea severity. American journal of orthodontics and dentofacial orthopedics 125 (5):548-555
14. Kim HJ, Hong S-N, Lee WH, Ahn J-C, Cha M-S, Rhee C-S, Kim J-W (2018) Soft palate cephalometric changes with a mandibular advancement device may be associated with polysomnographic improvement in obstructive sleep apnea. European Archives of Oto-Rhino-Laryngology 275 (7):1811-1817
15. Okuno K, Sasao Y, Nohara K, Sakai T, Pliska BT, Lowe AA, Ryan CF, Almeida FR (2016) Endoscopy evaluation to predict oral appliance outcomes in obstructive sleep apnoea. European Respiratory Journal 47 (5):1410-1419
16. Camañes-Gonzalvo S, Marco-Pitarch R, Plaza-Espín A, Puertas-Cuesta J, Agustín-Panadero R, Fons-Font A, Fons-Badal C, García-Selva M (2021) Correlation between Polysomnographic Parameters and Tridimensional Changes in the Upper Airway of Obstructive Sleep Apnea Patients Treated with Mandibular Advancement Devices. Journal of clinical medicine 10 (22). Doi:10.3390/jcm10225255
17. Gao X, Otsuka R, Ono T, Honda E-i, Sasaki T, Kuroda T (2004) Effect of titrated mandibular advancement and jaw opening on the upper airway in nonapneic men: a magnetic resonance imaging and cephalometric study. American journal of orthodontics and dentofacial orthopedics 125 (2):191-199
18. De Backer J, Vanderveken O, Vos W, Devolder A, Verhulst S, Verbraecken J, Parizel P, Braem M, Van de Heyning P, De Backer W (2007) Functional imaging using computational fluid dynamics to predict treatment success of mandibular advancement devices in sleep-disordered breathing. Journal of

biomechanics 40 (16):3708-3714
19. Tsuiki S, Lowe A, Almeida F, Kawahata N, Fleetham J (2004) Effects of mandibular advancement on airway curvature and obstructive sleep apnoea severity. European Respiratory Journal 23 (2):263-268
20. Ahlqvist J, Eliasson S, Welander U (1986) The effect of projection errors on cephalometric length measurements. The European Journal of Orthodontics 8 (3):141-148
21. Chan AS, Sutherland K, Schwab RJ, Zeng B, Petocz P, Lee RW, Darendeliler MA, Cistulli PA (2010) The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. Thorax 65 (8):726-732
22. Sutherland K, Deane SA, Chan AS, Schwab RJ, Ng AT, Darendeliler MA, Cistulli PA (2011) Comparative effects of two oral appliances on upper airway structure in obstructive sleep apnea. Sleep 34 (4):469-477
23. Ogawa T, Long J, Sutherland K, Chan AS, Sasaki K, Cistulli PA (2015) Effect of mandibular advancement splint treatment on tongue shape in obstructive sleep apnea. Sleep and Breathing 19 (3):857-863
24. Pahkala R, Seppä J, Myllykangas R, Tervaniemi J, Vartiainen V, Suominen A, Muraja-Murro A (2020) The impact of oral appliance therapy with moderate mandibular advancement on obstructive sleep apnea and upper airway volume. Sleep and Breathing 24 (3):865-873
25. Shi X, Lobbezoo F, Chen H, Rosenmöller B, Berkhout E, de Lange J, Aarab G (2023) Comparisons of the effects of two types of titratable mandibular advancement devices on respiratory parameters and upper airway dimensions in patients with obstructive sleep apnea: a randomized controlled trial. Clinical oral investigations. doi:10.1007/s00784-023-04945-z
26. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force (1999). Sleep 22 (5):667-689
27. de Ruiter M, Aarab G, de Vries N, Lobbezoo F, de Lange J (2020) A stepwise titration protocol for oral appliance therapy in positional obstructive sleep apnea patients: proof of concept. Sleep and Breathing:1-8
28. Benoist LBL, Verhagen M, Torensma B, van Maanen JP, de Vries N (2017) Positional therapy in patients with residual positional obstructive sleep apnea after upper airway surgery. Sleep and Breathing 21 (2):279-288. doi:10.1007/s11325-016-1397-x
29. de Ruiter MHT, Benoist LBL, de Vries N, de Lange J (2018) Durability of treatment effects of the Sleep Position Trainer versus oral appliance therapy in positional OSA: 12-month follow-up of a randomized controlled trial. Sleep and Breathing 22 (2):441-450. doi:10.1007/s11325-017-1568-4
30. Chen H, Aarab G, Parsa A, de Lange J, van der Stelt PF, Lobbezoo F (2016) Reliability of three-dimensional measurements of the upper airway on cone beam computed tomography images. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 122 (1):104-110
31. Chen H, Aarab G, de Ruiter MH, de Lange J, Lobbezoo F, van der Stelt PF (2016) Three-dimensional imaging of the upper airway anatomy in obstructive sleep apnea: a systematic review. Sleep medicine 21:19-27
32. Winer B (1971) Statistical Principles in Experimental Design: 2d Ed. McGraw-Hill,
33. Holm S (1979) A simple sequentially rejective multiple test procedure. Scandinavian journal of statistics:65-70
34. Thabane L, Mbuagbaw L, Zhang S, Samaan Z, Marcucci M, Ye C, Thabane M, Giangregorio L, Dennis B, Kosa D (2013) A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. BMC medical research methodology 13 (1):1-12
35. Koo TK, Li MY (2016) A guideline of selecting and reporting intraclass correlation coefficients for reliability research. Journal of chiropractic medicine 15 (2):155-163
36. Camacho M, Capasso R, Schendel S (2014) Airway changes in obstructive sleep apnoea patients associated with a supine versus an upright position examined using cone beam computed tomography. The Journal of Laryngology & Otology 128 (9):824-830
37. Cohen J (2013) Statistical power analysis for the behavioral sciences. Academic press,
38. Edwards BA, Andara C, Landry S, Sands SA, Joosten SA, Owens RL, White DP, Hamilton GS, Wellman A (2016) Upper-airway collapsibility and loop gain predict the response to oral appliance therapy in patients with obstructive sleep apnea. American journal of respiratory and critical care medicine 194 (11):1413-1422
39. Op de Beeck S, Dieltjens M, Azarbarzin A, Willemen M, Verbraecken J, Braem MJ, Wellman A, Sands SA, Vanderveken OM (2020) Mandibular Advancement Device Treatment Efficacy is Associated with Polysomnographic Endotypes. Annals of the American Thoracic Society (ja)
40. Sam K, Lam B, Ooi C, Cooke M, Ip M (2006) Effect of a non-adjustable oral appliance on upper airway morphology in obstructive sleep apnoea. Respiratory medicine 100 (5):897-902
41. Marco-Pitarch R, Selva-García M, Plaza-Espín A, Puertas-Cuesta J, Agustín-Panadero R, Fernández-Julián E, Marco-Algarra J, Fons-Font A (2021) Dimensional analysis of the upper airway in obstructive sleep apnea syndrome patients treated with mandibular advancement device: a bi and three-dimensional evaluation. Journal of Oral Rehabilitation
42. Liu Y, Lowe AA, Fleetham JA, Park YC (2001) Cephalometric and physiologic predictors of the efficacy of

an adjustable oral appliance for treating obstructive sleep apnea. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics 120 (6):639-647
43. Milano F, Billi MC, Marra F, Sorrenti G, Gracco A, Bonetti GA (2013) Factors associated with the efficacy of mandibular advancing device treatment in adult OSA patients. International orthodontics 11 (3):278-289. doi:10.1016/j.ortho.2013.05.006
44. Mostafiz W, Dalci O, Sutherland K, Malhotra A, Srinivasan V, Darendeliler MA, Cistulli PA (2011) Influence of oral and craniofacial dimensions on mandibular advancement splint treatment outcome in patients with obstructive sleep apnea. Chest 139 (6):1331-1339. doi:10.1378/chest.10-2224
45. Ng AT, Darendeliler MA, Petocz P, Cistulli PA (2012) Cephalometry and prediction of oral appliance treatment outcome. Sleep & breathing = Schlaf & Atmung 16 (1):47-58. doi:10.1007/s11325-011-0484-2
46. Sutherland K, Cistulli P (2011) Mandibular advancement splints for the treatment of sleep apnea syndrome. Swiss medical weekly 141 (3940)
47. Vroegop AV, Vanderveken OM, Van de Heyning PH, Braem MJ (2012) Effects of vertical opening on pharyngeal dimensions in patients with obstructive sleep apnoea. Sleep medicine 13 (3):314-316
48. Barbero M, Flores-Mir C, Blanco JC, Nuño VC, Casellas JB, Girado JLC, Amezaga JA, De Carlos F (2020) Tridimensional upper airway assessment in male patients with OSA using oral advancement devices modifying their vertical dimension. Journal of Clinical Sleep Medicine 16 (10):1721-1729
49. Norrhem N, Marklund M (2016) An oral appliance with or without elastic bands to control mouth opening during sleep-a randomized pilot study. Sleep & breathing = Schlaf & Atmung 20 (3):929-938. doi:10.1007/s11325-016-1312-5
50. Milano F, Mutinelli S, Sutherland K, Milioli G, Scaramuzzino G, Cortesi A, Siciliani G, Lombardo L, Cistulli P (2018) Influence of Vertical Mouth Opening on Oral Appliance Treatment Outcome in Positional Obstructive Sleep Apnea. Journal of Dental Sleep Medicine 05:17-23. doi:10.15331/jdsm.6918

Chapter 7

General Discussion

It has been well established that an impaired upper airway morphology is a key pathophysiologic factor of obstructive sleep apnea (OSA) [1,2]. However, there are still many aspects where our understanding of the role of the upper airway morphology in the pathogenesis and treatment of OSA remains unclear. Therefore, the general research aim of this thesis was to investigate the role of the upper airway morphology in the pathogenesis and treatment of different OSA phenotypes and in the treatment effects of mandibular advancement device (MAD) therapy. In this chapter, some methodological aspects, the main research outcomes, and the clinical implications of the chapters are discussed, and suggestions for future research are made.

Methodological considerations

The upper airway patency is affected by the activities of the upper airway dilator muscles, which can stiffen and enlarge the upper airway by their contractions [3-5]. These activities are coordinated by several reflex mechanisms in awake state and are significantly reduced in sleep state [6,7]. Therefore, in this thesis, the upper airway morphology as assessed by CBCT imaging is affected by the dilator muscle activities, and therefore may not precisely reflect the impairment in the morphology. The pharyngeal critical closing pressure (Pcrit), defined as the pressure inside the upper airway at which the airway collapses, is the gold standard to qualify the upper airway collapsibility [8]. Among various Pcrit methods, the passive Pcrit technique is measured when the activities of the upper airway dilator muscles are minimized [9]. Therefore, the passive Pcrit has been recommended to represent the anatomical impairment of the upper airway when assessing the pathogenesis of OSA, which is expected to enhance the OSA phenotyping and improve the treatment efficacy of therapies targeting the anatomical factors, such as the MAD therapy [10]. However, the passive Pcrit technique is still limited in routine clinical practice due to its complexity [8]. New emerging surrogates, for example, the use of peak inspiratory flow measurements during routine overnight polysomnography (PSG), are promising to simplify the estimation of Pcrit [11]. Future studies are still needed to validate the simplified techniques to assess the role of upper airway morphology in OSA pathogenesis and treatment.

MAD therapy is recommended as a primary treatment option in patients with mild and moderate OSA, and in patients with severe OSA who refuse or are unable to tolerate CPAP therapy [12,13]. The treatment effects of MAD in **Chapters 5** and **6** were assessed in a group of patients with mild to moderate OSA. In a study by Mosca et al. [14], the treatment success rate of MAD for mild (100%) and moderate

(87%) groups was higher than for the severe group (64%), indicating that MAD therapy is less effective in patients with severe OSA. The suboptimal treatment effects of MAD in the severe OSA group may be related to the differed pathogenesis between severe OSA and mild-to-moderate OSA [15]. Compared to mild-to-moderate OSA group, the severe OSA group typically has a smaller cross-sectional area of the upper airway and a more collapsible upper airway [16,17]. For the non-anatomical factors, although data are limited, the high loop gain and the low arousal threshold may be more evident in patients with mild-to-moderate OSA than in those with severe OSA [18,19]. In other words, the severe OSA group tends to be less heterogeneous in its pathogenesis compared to mild-to-moderate OSA group, with a severely impaired upper airway morphology as the main pathophysiological trait [15]. As MAD usually addresses moderate upper airway collapsibility, MAD therapy may not sufficiently address the upper airway collapse of the severe OSA group [20]. However, in a multicenter study [21], MAD decreased AHI by 67 ± 22% after one month of treatment for severe OSA, with half of the patients having an AHI of <10 events/h and 20% of patients having an AHI of <5 events/h after the treatment. Therefore, MAD therapy can also be effective in some severe patients with OSA, but a method of selecting responsive patients is still lacking. Currently, studies of MAD effects on patients with severe OSA are still relatively scarce, which calls for more future studies on MAD therapy in severe OSA groups.

OSA phenotypes

Even though positional OSA (POSA) has its unique clinical manifestation and treatment recommendation, it is not clear whether this group has its unique pathophysiologic traits as compared with non-POSA (NPOSA) group [22]. When the study of **Chapter 2** recruited both groups with similar OSA severity as indicated by AHI, both groups showed similar anatomical balance and shape of the upper airway. Based on these findings, it can be speculated that the anatomical treatment modalities, e.g., the MAD therapy, may result in similar treatment efficacy in POSA and NPOSA groups. Currently, studies regarding the efficacy of MAD treatment in POSA vs NPOSA groups are inconclusive. Some studies have suggested that MAD is more effective in the POSA group [23,24], while a large-scale study by Sutherland et al. [25] has suggested that MAD is more effective in the NPOSA group. Different MAD types and study samples may explain the different results. Furthermore, a recent study has suggested that MAD treatment effects are similar in POSA and NPOSA groups [26], which may support our non-significant findings in the upper airway morphology between both groups. In addition to anatomical factors, some non-anatomical factors have been suggested to be different between both groups,

such as upper airway dilator muscle activities and lung volume [27,28]. However, in previous studies, samples included mainly severe OSA or both groups had unmatched AHI, which may bias the results. Regardless of the underlying mechanism, positional therapy (PT) is recommended for the POSA group, as it helps to avoid sleeping in the supine position [29,30]. However, POSA may change to NPOSA with weight gain, and the possible mechanism is related to the accumulation of adipose tissues in the lateral wall of the upper airway, which worsens the AHI in lateral position [31]. Therefore, monitoring is needed when PT is prescribed [32]. Future studies are needed to better illustrate the pathogenesis of both groups, which is important for the treatment guidelines.

When investigating the differences in the pathogenesis of OSA between races, several challenges have been acknowledged. First, although Asian OSA groups have more skeletal restrictions (e.g., a smaller maxilla, a smaller and retro-positioned mandible) compared to Caucasian OSA groups [33-36], the normative values of some skeletal structures are also different between Asian and Caucasian general populations [37,38]. Therefore, to what extent the skeletal restrictions predispose the Asian population to OSA is not known [39]. Second, studies have consistently shown that Asians have lower BMI than Caucasians at similar levels of AHI [33-36]. However, a direct inter-race comparison of the absolute BMI may not be appropriate [40], considering that Asians have lower BMI but higher percent body fat than Caucasians [41]. Regarding this issue, World Health Organization (WHO) has suggested that the universal BMI cut-off points (25 and 30 kg/m^2 for overweight and obesity, respectively) are not suitable for Asian populations [42]. However, there is no recommendation for new BMI cut-off points for Asians [42]. A study by Genta et al. [39] has suggested that when comparing Japanese descendants with Caucasians, ethnicity is an independent predictor for AHI; however, when adjusting the criteria for obesity (25 and 30 kg/ m^2 for Japanese descendants and Caucasians, respectively), being Asian was no longer significantly associated with OSA severity. Third, as noted in our study and previous studies, the socioeconomic status and cultural background may influence the referral pattern of OSA patients to a sleep clinic, and Chinese OSA patients may go to see a sleep physician only when the disease is already severe, resulting in a high proportion of severe OSA in Chinese OSA sample recruited from a sleep clinic [34]. This may be one of the reasons that the data from sleep clinics and epidemiological studies are sometimes contrary. For example, a study of Lee et al. [34] has suggested that one unit of BMI increase will cause more AHI increase in Asian sample as compared to a Caucasian one, while epidemiological studies indicate that the odds of having OSA for each standard deviation of BMI increment is lower in Chinese patients compared to the Wisconsin cohort (odds ratio 2.42 vs 4.19) [43,44].

To reduce the influence of the afore-mentioned problems, when conducting the inter-race study in **Chapter 3,** we used the anatomical balance as the primary outcome variable (a synthetic effect of soft and hard tissues), and we only included mild-to-moderate OSA patients. The result indicates no significant difference in the anatomical balance of the upper airway between Dutch and Chinese groups with mild to moderate OSA, suggesting that the anatomical predisposition to upper airway obstruction may be similar between both groups. Based on the results, it may be further hypothesized that the efficacy of MAD therapy may be similar in both races. A study by Li et al. [45] used a remotely controlled mandibular positioner for MAD titration and suggested that the success rate of MAD was higher in the Chinese OSA group than in the Caucasian OSA group. Currently, studies comparing the treatment efficacy of MAD between races are still lacking, and more research is needed. Taking these aspects together, obesity, craniofacial structures, and race seem to interact in the pathogenesis of OSA. However, stronger evidence is still needed to clarify the racial difference in OSA pathogenesis and treatment effects.

Individuals with Class II high-angle malocclusion (a craniofacial abnormality with mandible retrognathia and mandibular vertical excess) may not have OSA at a younger age, however, the risk of developing OSA may be higher with ageing and the accumulation of fat tissues surrounding the upper airway compared to individuals with a normal occlusion and craniofacial structures [46]. Hence, it would be important to identify and treat these abnormalities in an attempt to prevent OSA in those individuals [47]. **Chapter 4** of this thesis has suggested that miniscrew-assisted premolar extractions treatment can result in the counterclockwise rotation of the mandible in young adults with Class II high-angle malocclusion, which can subsequently increase the upper airway dimensions. The mechanism between the mandibular rotation and upper airway changes would be related to the muscular connection, such as the tongue. Furthermore, studies have also suggested that rapid maxillary expansion achieved by orthodontic and orthopedic procedures can help to improve OSA in children [48,49]. However, to the best of our knowledge, there is no solid evidence to support that such orthodontic and orthopedic treatments could decrease the risk of OSA development in the long-term. Therefore, whether the enlargement of the upper airway contributes to the prevention of OSA in the long-term should be determined in future longitudinal studies.

MAD therapy

While a wide range of different types of MAD is available currently, the custom-made titratable MAD devices are the recommended ones in clinical practice [50,51].

The key design feature of titratable custom-made MADs is the protrusion of the mandible. However, they could differ in many aspects, such as size, construction material, amount of occlusal coverage, articulating site (e.g., dental bilateral or midline), and the allowance of vertical and lateral jaw movement [52]. **Chapter 5** indicates that an MAD with a free vertical opening and an MAD with a limited vertical opening have similar effects on upper airway dimensions and treatment efficacy in decreasing the AHI. The results are consistent with a recent systematic review suggesting that the different design features of different customized MADs have no significant impact on treatment effects [53]. However, the different designs may affect the comfort and preference of patients, which also impact adherence with the treatment [53,54]. For example, a patient with sleep bruxism may prefer an MAD that allows some degree of lateral or vertical opening [53], while other patients may prefer to restrict the freedom of their mouth opening during sleep with elastic bands [55]. A patient's adherence is vital to MAD treatment success, as there is an effect on OSA only when the MAD is worn. This led to the introduction of the concept of mean disease alleviation (MDA), which can represent the overall therapeutic effectiveness, calculated by timing the objective adherence and therapeutic efficacy [56]. By using the MDA concept, there is an equivalent therapeutic effectiveness of MAD and CPAP therapies in AHI reduction, as the superiority of CPAP efficacy in reducing AHI is compromised by its lower adherence [56,57]. Therefore, a higher adherence can improve the treatment effectiveness of the MAD therapy. However, there currently is insufficient evidence for the optimal MAD designs in patient's characteristics [53]. Therefore, more research in the future is needed on the preference, comfort, and adherence to MADs with different designs in patients with OSA.

Being able to predict which patients will respond to MAD therapy could avoid ineffective treatment in the early stage and avoid waste of medical resources, which is a priority in research and clinic. Following **Chapter 5,** we further conducted a study to investigate the underlying mechanism of different responses to MAD therapy. Considering that the primary working mechanism of MAD is related to upper airway enlargement, we hypothesized that different responses to MAD therapy may be explained by different effects on upper airway dimensions. However, the results of **Chapter 6** suggest that the effect of MAD on upper airway dimensions is similar between responders and non-responders. For non-responders, non-anatomical factors (e.g., a high loop gain) may be involved in the OSA pathogenesis [58,59]. Therefore, a good prediction model needs a comprehensive assessment of anatomical and non-anatomical factors, and a reliable way of phenotyping. That is also true for improving the treatment efficacy for other patient-centered outcomes of OSA, such as daytime sleepiness and hypertension [60]. By using

cluster analysis to identify OSA subtypes with various combinations of symptoms and comorbidities, a study of Ye et al. [61] has suggested 3 distinct groups: 1. disturbed sleep group (33%), 2. minimally symptomatic group (25%), and 3. excessive daytime sleepiness group (43%). Within these groups, group 2 had the highest chance of developing comorbid hypertension and cardiovascular disease [61]. Notably, these 3 groups do not differ significantly in sex, BMI, or AHI [61]. The findings represent an important step in phenotyping patients, although more research on the reproducibility and stability of these clusters within and across studies is still needed [62]. Thus, phenotyping patients with OSA into more homogeneous groups according to disease specific pathophysiological factors and clinical features seems to hold promise to further improve treatment efficacy and enhance precision medicine [63].

Future directions

As emphasized both in this thesis and in the literature, in addition to anatomical factors, elucidating the underlying mechanism of non-anatomical factors for upper airway collapse is one of the key steps to realize precision medicine of OSA. Some commonly investigated non-anatomical factors are the arousal threshold (premature awakening to mild airway narrowing), loop gain (unstable control of breathing), and muscle responsiveness [10,1]. Besides, factors such as small lung volume, arousal intensity, and redistribution of body fluid seem to be important in the pathogenesis of OSA as well [64]. Nonetheless, these concepts have not been widely adopted into clinical practice, because the gold standard to assess these factors is labor-intensive and complex [65]. Recent advances have simplified the measures of arousal threshold [66,67], loop gain [68], and muscle responsiveness [69] by using a PSG recording or a CPAP. A future priority will be to continue to refine and enhance the understanding of the pathogenesis of OSA and integrate new insights into clinical practice [70].

The participatory aspect of precision medicine turns a patient from a passive receiver of care into an active manager of his or her wellness [47]. However, the current clinical management of OSA offers patients limited participatory healthcare options [71]. A recent RCT study has indicated an improvement in adherence to CPAP treatment through the application of participatory care using a web-based technology [72], which is an excellent example of participatory approaches. To select the best therapy for each OSA patient, carefully tested clinical algorithms which analyze all relevant data will likely be developed [71]. To achieve this, the active participation of patients is needed to allow more clinically relevant data to

be collected in a digital platform [71,73]. Therefore, improving the participation of patients is an important direction for future OSA management.

Conclusions

The upper airway morphology does not play a significant role in the pathogenesis of different OSA phenotypes and in the treatment effects of MAD. Future research involving both anatomical and non-anatomical factors is needed to better understand the pathogenesis and treatment outcomes of OSA, which is important to realize precision medicine.

References

1. Eckert DJ (2018) Phenotypic approaches to obstructive sleep apnoea–new pathways for targeted therapy. Sleep medicine reviews 37:45-59
2. Schwab RJ (2003) Pro: sleep apnea is an anatomic disorder. Am J Respir Crit Care Med 168 (3):270-271; discussion 273. doi:10.1164/rccm.2305014
3. Pierce R, White D, Malhotra A, Edwards JK, Kleverlaan D, Palmer L, Trinder J (2007) Upper airway collapsibility, dilator muscle activation and resistance in sleep apnoea. The European respiratory journal 30 (2):345-353. doi:10.1183/09031936.00063406
4. Yang C, Woodson BT (2003) Upper airway physiology and obstructive sleep-disordered breathing. Otolaryngol Clin North Am 36 (3):409-421. doi:10.1016/s0030-6665(03)00017-3
5. Fogel RB, Malhotra A, White DP (2004) Sleep. 2: pathophysiology of obstructive sleep apnoea/hypopnoea syndrome. Thorax 59 (2):159-163. doi:10.1136/thorax.2003.015859
6. Fogel RB, Trinder J, White DP, Malhotra A, Raneri J, Schory K, Kleverlaan D, Pierce RJ (2005) The effect of sleep onset on upper airway muscle activity in patients with sleep apnoea versus controls. The Journal of physiology 564 (Pt 2):549-562. doi:10.1113/jphysiol.2005.083659
7. Jordan AS, White DP (2008) Pharyngeal motor control and the pathogenesis of obstructive sleep apnea. Respiratory physiology & neurobiology 160 (1):1-7. doi:10.1016/j.resp.2007.07.009
8. Kazemeini E, Van de Perck E, Dieltjens M, Willemen M, Verbraecken J, Op de Beeck S, Vanderveken OM (2022) Critical to Know Pcrit: A Review on Pharyngeal Critical Closing Pressure in Obstructive Sleep Apnea. Frontiers in neurology 13:775709. doi:10.3389/fneur.2022.775709
9. Schwartz AR, O'Donnell CP, Baron J, Schubert N, Alam D, Samadi SD, Smith PL (1998) The hypotonic upper airway in obstructive sleep apnea: role of structures and neuromuscular activity. Am J Respir Crit Care Med 157 (4 Pt 1):1051-1057. doi:10.1164/ajrccm.157.4.9706067
10. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A (2013) Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. American journal of respiratory and critical care medicine 188 (8):996-1004
11. Azarbarzin A, Sands SA, Taranto-Montemurro L, Oliveira Marques MD, Genta PR, Edwards BA, Butler J, White DP, Wellman A (2017) Estimation of Pharyngeal Collapsibility During Sleep by Peak Inspiratory Airflow. Sleep 40 (1). doi:10.1093/sleep/zsw005
12. Epstein LJ, Kristo D, Strollo PJ, Jr., Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM, Weinstein MD (2009) Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 5 (3):263-276
13. Sharples LD, Clutterbuck-James AL, Glover MJ, Bennett MS, Chadwick R, Pittman MA, Quinnell TG (2016) Meta-analysis of randomised controlled trials of oral mandibular advancement devices and continuous positive airway pressure for obstructive sleep apnoea-hypopnoea. Sleep Med Rev 27:108-124. doi:10.1016/j.smrv.2015.05.003
14. Mosca EV, Bruehlmann S, Zouboules SM, Chiew AE, Westersund C, Hambrook DA, Jahromi SAZ, Grosse J, Topor ZL, Charkhandeh S, Remmers JE (2022) In-home mandibular repositioning during sleep using MATRx plus predicts outcome and efficacious positioning for oral appliance treatment of obstructive sleep apnea. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 18 (3):911-919. doi:10.5664/jcsm.9758
15. Edwards BA, Eckert DJ, Jordan AS (2017) Obstructive sleep apnoea pathogenesis from mild to severe: is it all the same? Respirology 22 (1):33-42
16. Yucel A, Unlu M, Haktanir A, Acar M, Fidan F (2005) Evaluation of the upper airway cross-sectional area changes in different degrees of severity of obstructive sleep apnea syndrome: cephalometric and dynamic CT study. American journal of neuroradiology 26 (10):2624-2629
17. Gold AR, Marcus CL, Dipalo F, Gold MS (2002) Upper airway collapsibility during sleep in upper airway resistance syndrome. Chest 121 (5):1531-1540
18. Edwards BA, Eckert DJ, McSharry DG, Sands SA, Desai A, Kehlmann G, Bakker JP, Genta PR, Owens RL, White DP (2014) Clinical predictors of the respiratory arousal threshold in patients with obstructive sleep apnea. American journal of respiratory and critical care medicine 190 (11):1293-1300
19. Joosten SA, Hamza K, Sands S, Turton A, Berger P, Hamilton G (2012) Phenotypes of patients with mild to moderate obstructive sleep apnoea as confirmed by cluster analysis. Respirology 17 (1):99-107
20. Ng AT, Gotsopoulos H, Qian J, Cistulli PA (2003) Effect of oral appliance therapy on upper airway collapsibility in obstructive sleep apnea. Am J Respir Crit Care Med 168 (2):238-241. doi:10.1164/rccm.200211-1275OC
21. Byun JI, Kim D, Ahn SJ, Yang KI, Cho YW, Cistulli PA, Shin WC (2020) Efficacy of Oral Appliance Therapy as a First-Line Treatment for Moderate or Severe Obstructive Sleep Apnea: A Korean Prospective Multicenter Observational Study. Journal of clinical neurology (Seoul, Korea) 16 (2):215-221. doi:10.3988/

jcn.2020.16.2.215
22. Joosten SA, O'Driscoll DM, Berger PJ, Hamilton GS (2014) Supine position related obstructive sleep apnea in adults: pathogenesis and treatment. Sleep medicine reviews 18 (1):7-17
23. Chung JW, Enciso R, Levendowski DJ, Morgan TD, Westbrook PR, Clark GT (2010) Treatment outcomes of mandibular advancement devices in positional and nonpositional OSA patients. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 109 (5):724-731
24. Marklund M, Persson M, Franklin KA (1998) Treatment success with a mandibular advancement device is related to supine-dependent sleep apnea. Chest 114 (6):1630-1635
25. Sutherland K, Takaya H, Qian J, Petocz P, Ng AT, Cistulli PA (2015) Oral Appliance Treatment Response and Polysomnographic Phenotypes of Obstructive Sleep Apnea. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 11 (8):861-868. doi:10.5664/jcsm.4934
26. Bosschieter PFN, Vonk PE, de Vries N, Ravesloot MJL (2022) Position-dependent obstructive sleep apnea and its influence on treatment success of mandibular advancement devices. Sleep & breathing = Schlaf & Atmung 26 (3):1237-1243. doi:10.1007/s11325-021-02488-9
27. Joosten SA, Edwards BA, Wellman A, Turton A, Skuza EM, Berger PJ, Hamilton GS (2015) The effect of body position on physiological factors that contribute to obstructive sleep apnea. Sleep 38 (9):1469-1478
28. Joosten SA, Sands SA, Edwards BA, Hamza K, Turton A, Lau KK, Crossett M, Berger PJ, Hamilton GS (2015) Evaluation of the role of lung volume and airway size and shape in supine-predominant obstructive sleep apnoea patients. Respirology 20 (5):819-827
29. Beyers J, Vanderveken OM, Kastoer C, Boudewyns A, De Volder I, Van Gastel A, Verbraecken JA, De Backer WA, Braem MJ, Van de Heyning PH, Dieltjens M (2019) Treatment of sleep-disordered breathing with positional therapy: long-term results. Sleep & breathing = Schlaf & Atmung 23 (4):1141-1149. doi:10.1007/s11325-019-01792-9
30. Barnes H, Edwards BA, Joosten SA, Naughton MT, Hamilton GS, Dabscheck E (2017) Positional modification techniques for supine obstructive sleep apnea: A systematic review and meta-analysis. Sleep Med Rev 36:107-115. doi:10.1016/j.smrv.2016.11.004
31. Oksenberg A, Dynia A, Nasser K, Gadoth N (2012) Obstructive sleep apnoea in adults: body postures and weight changes interactions. J Sleep Res 21 (4):402-409. doi:10.1111/j.1365-2869.2011.00988.x
32. Chou YT, Yang TM, Lin CK, Huang SY, Tsai YH, Chang JF, Hou YJ, Lin YC (2017) Pay attention to treating a subgroup of positional obstructive sleep apnea patients. Journal of the Formosan Medical Association = Taiwan yi zhi 116 (5):359-365. doi:10.1016/j.jfma.2016.06.007
33. Liu Y, Lowe AA, Zeng X, Fu M, Fleetham JA (2000) Cephalometric comparisons between Chinese and Caucasian patients with obstructive sleep apnea. American Journal of Orthodontics & Dentofacial Orthopedics 117 (4):479-485
34. Lee RW, Vasudavan S, Hui DS, Prvan T, Petocz P, Darendeliler MA, Cistulli PA (2010) Differences in craniofacial structures and obesity in Caucasian and Chinese patients with obstructive sleep apnea. Sleep 33 (8):1075-1080
35. Schorr F, Kayamori F, Hirata RP, Danzi-Soares NJ, Gebrim EM, Moriya HT, Malhotra A, Lorenzi-Filho G, Genta PR (2016) Different craniofacial characteristics predict upper airway collapsibility in Japanese-Brazilian and white men. Chest 149 (3):737-746
36. Sutherland K, Lee RW, Cistulli PA (2012) Obesity and craniofacial structure as risk factors for obstructive sleep apnoea: impact of ethnicity. Respirology 17 (2):213-222
37. Ioi H, Nakata S, Nakasima A, Counts AL (2007) Comparison of cephalometric norms between Japanese and Caucasian adults in antero-posterior and vertical dimension. Eur J Orthod 29 (5):493-499. doi:10.1093/ejo/cjm059
38. Gu Y, McNamara JA, Jr., Sigler LM, Baccetti T (2011) Comparison of craniofacial characteristics of typical Chinese and Caucasian young adults. Eur J Orthod 33 (2):205-211. doi:10.1093/ejo/cjq054
39. Genta PR, Marcondes BF, Danzi NJ, Lorenzi-Filho G (2008) Ethnicity as a risk factor for obstructive sleep apnea: comparison of Japanese descendants and white males in São Paulo, Brazil. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas 41 (8):728-733. doi:10.1590/s0100-879x2008000800015
40. Genta PR, Lorenzi-Filho G (2011) Sleep apnoea in Asians and Caucasians: comparing apples and oranges. The European respiratory journal 37 (6):1537-1538; author reply 1538-1539. doi:10.1183/09031936.00200510
41. Wang J, Thornton JC, Russell M, Burastero S, Heymsfield S, Pierson RN, Jr. (1994) Asians have lower body mass index (BMI) but higher percent body fat than do whites: comparisons of anthropometric measurements. The American journal of clinical nutrition 60 (1):23-28. doi:10.1093/ajcn/60.1.23
42. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies (2004). Lancet (London, England) 363 (9403):157-163. doi:10.1016/s0140-6736(03)15268-3
43. Ip MS, Lam B, Lauder IJ, Tsang KW, Chung KF, Mok YW, Lam WK (2001) A community study of sleep-disordered breathing in middle-aged Chinese men in Hong Kong. Chest 119 (1):62-69. doi:10.1378/

chest.119.1.62
44. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S (1993) The occurrence of sleep-disordered breathing among middle-aged adults. The New England journal of medicine 328 (17):1230-1235. doi:10.1056/nejm199304293281704
45. Li WY, Masse JF, Gakwaya S, Zhao Z, Wang W, Sériès F (2022) Differences in Predicted Therapeutic Outcome of Mandibular Advancement Determined by Remotely Controlled Mandibular Positioner in Canadian and Chinese Apneic Patients. Nat Sci Sleep 14:1611-1622. doi:10.2147/nss.s377758
46. Neelapu BC, Kharbanda OP, Sardana HK, Balachandran R, Sardana V, Kapoor P, Gupta A, Vasamsetti S (2017) Craniofacial and upper airway morphology in adult obstructive sleep apnea patients: A systematic review and meta-analysis of cephalometric studies. Sleep Med Rev 31:79-90. doi:10.1016/j.smrv.2016.01.007
47. Lim DC, Sutherland K, Cistulli PA, Pack AI (2017) P4 medicine approach to obstructive sleep apnoea. Respirology 22 (5):849-860
48. Camacho M, Chang ET, Song SA, Abdullatif J, Zaghi S, Pirelli P, Certal V, Guilleminault C (2017) Rapid maxillary expansion for pediatric obstructive sleep apnea: A systematic review and meta-analysis. The Laryngoscope 127 (7):1712-1719
49. Ngiam J, Cistulli PA (2015) Dental treatment for paediatric obstructive sleep apnea. Paediatric respiratory reviews 16 (3):174-181
50. Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, Chervin RD (2015) Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015: an American Academy of Sleep Medicine and American Academy of Dental Sleep Medicine clinical practice guideline. Journal of clinical sleep medicine 11 (7):773-827
51. Johal A, Agha B (2018) Ready-made versus custom-made mandibular advancement appliances in obstructive sleep apnea: A systematic review and meta-analysis. Journal of sleep research 27 (6):e12660
52. Sutherland K, Cistulli P (2011) Mandibular advancement splints for the treatment of sleep apnea syndrome. Swiss medical weekly 141:w13276. doi:10.4414/smw.2011.13276
53. Venema JAU, Rosenmöller BR, De Vries N, de Lange J, Aarab G, Lobbezoo F, Hoekema A (2021) Mandibular advancement device design: A systematic review on outcomes in obstructive sleep apnea treatment. Sleep medicine reviews 60:101557
54. Timothy GQ, Maxine B, Jake J, Abigail LC-J, Michael GD, Ian ES, Nicholas O, Marcus AP, Malcolm C, Rebecca C, Mary JM, Matthew JG, Julia AF-R, Linda DS (2014) A crossover randomised controlled trial of oral mandibular advancement devices for obstructive sleep apnoea-hypopnoea (TOMADO). Thorax 69 (10):938. doi:10.1136/thoraxjnl-2014-205464
55. Norrhem N, Marklund M (2016) An oral appliance with or without elastic bands to control mouth opening during sleep-a randomized pilot study. Sleep & breathing = Schlaf & Atmung 20 (3):929-938. doi:10.1007/s11325-016-1312-5
56. Vanderveken OM, Dieltjens M, Wouters K, De Backer WA, Van de Heyning PH, Braem MJ (2013) Objective measurement of compliance during oral appliance therapy for sleep-disordered breathing. Thorax 68 (1):91-96
57. Francis CE, Quinnell T (2021) Mandibular Advancement Devices for OSA: An Alternative to CPAP? Pulmonary therapy 7 (1):25-36. doi:10.1007/s41030-020-00137-2
58. Edwards BA, Andara C, Landry S, Sands SA, Joosten SA, Owens RL, White DP, Hamilton GS, Wellman A (2016) Upper-airway collapsibility and loop gain predict the response to oral appliance therapy in patients with obstructive sleep apnea. American journal of respiratory and critical care medicine 194 (11):1413-1422
59. Op de Beeck S, Dieltjens M, Azarbarzin A, Willemen M, Verbraecken J, Braem MJ, Wellman A, Sands SA, Vanderveken OM (2020) Mandibular Advancement Device Treatment Efficacy is Associated with Polysomnographic Endotypes. Annals of the American Thoracic Society (ja)
60. Marklund M, Braem MJA, Verbraecken J (2019) Update on oral appliance therapy. European respiratory review : an official journal of the European Respiratory Society 28 (153). doi:10.1183/16000617.0083-2019
61. Ye L, Pien GW, Ratcliffe SJ, Björnsdottir E, Arnardottir ES, Pack AI, Benediktsdottir B, Gislason T (2014) The different clinical faces of obstructive sleep apnoea: a cluster analysis. The European respiratory journal 44 (6):1600-1607. doi:10.1183/09031936.00032314
62. Zinchuk A, Yaggi HK (2020) Phenotypic subtypes of OSA: a challenge and opportunity for precision medicine. Chest 157 (2):403-420
63. Zinchuk AV, Gentry MJ, Concato J, Yaggi HK (2017) Phenotypes in obstructive sleep apnea: A definition, examples and evolution of approaches. Sleep Med Rev 35:113-123. doi:10.1016/j.smrv.2016.10.002
64. Sutherland K, Cistulli PA (2015) Recent advances in obstructive sleep apnea pathophysiology and treatment. Sleep and Biological Rhythms 13 (1):26-40
65. Malhotra A, Mesarwi O, Pepin J-L, Owens RL (2020) Endotypes and phenotypes in obstructive sleep apnea. Current opinion in pulmonary medicine 26 (6):609

66. Edwards BA, Eckert DJ, McSharry DG, Sands SA, Desai A, Kehlmann G, Bakker JP, Genta PR, Owens RL, White DP, Wellman A, Malhotra A (2014) Clinical predictors of the respiratory arousal threshold in patients with obstructive sleep apnea. Am J Respir Crit Care Med 190 (11):1293-1300. doi:10.1164/rccm.201404-0718OC
67. Sands SA, Terrill PI, Edwards BA, Taranto Montemurro L, Azarbarzin A, Marques M, de Melo CM, Loring SH, Butler JP, White DP, Wellman A (2018) Quantifying the Arousal Threshold Using Polysomnography in Obstructive Sleep Apnea. Sleep 41 (1). doi:10.1093/sleep/zsx183
68. Terrill PI, Edwards BA, Nemati S, Butler JP, Owens RL, Eckert DJ, White DP, Malhotra A, Wellman A, Sands SA (2015) Quantifying the ventilatory control contribution to sleep apnoea using polysomnography. The European respiratory journal 45 (2):408-418. doi:10.1183/09031936.00062914
69. Sands SA, Edwards BA, Terrill PI, Taranto-Montemurro L, Azarbarzin A, Marques M, Hess LB, White DP, Wellman A (2018) Phenotyping Pharyngeal Pathophysiology using Polysomnography in Patients with Obstructive Sleep Apnea. Am J Respir Crit Care Med 197 (9):1187-1197. doi:10.1164/rccm.201707-1435OC
70. Pépin J-L, Eastwood P, Eckert DJ (2022) Novel avenues to approach non-CPAP therapy and implement comprehensive obstructive sleep apnoea care. European Respiratory Journal 59 (6)
71. Arnardottir ES, Islind AS, Óskarsdóttir M, Ólafsdóttir KA, August E, Jónasdóttir L, Hrubos-Strøm H, Saavedra JM, Grote L, Hedner J (2022) The Sleep Revolution project: the concept and objectives. Journal of Sleep Research 31 (4):e13630
72. Kuna ST, Shuttleworth D, Chi L, Schutte-Rodin S, Friedman E, Guo H, Dhand S, Yang L, Zhu J, Bellamy SL (2015) Web-based access to positive airway pressure usage with or without an initial financial incentive improves treatment use in patients with obstructive sleep apnea. Sleep 38 (8):1229-1236
73. Lavigne G, Herrero Babiloni A, Beetz G, Dal Fabbro C, Sutherland K, Huynh N, Cistulli P (2020) Critical issues in dental and medical management of obstructive sleep apnea. Journal of dental research 99 (1):26-35

Chapter 8

Summary

OSA is a highly prevalent sleep-related breathing disorder, which is characterized by repetitive complete and/or partial obstructions of the upper airway that are often related to oxygen desaturations and arousals from sleep. The prevalence of OSA is estimated to be 14% in men and 5% in women in the general adult population. OSA is associated with several serious adverse health consequences, such as cognitive impairment, cardiovascular disease, and diabetes.

OSA is a heterogeneous disorder in its pathogenesis, with a complicated interaction of both anatomical (upper airway) and non-anatomical factors. Current evidence supports that the impaired upper airway morphology is likely the fundamental pathophysiological trait of OSA. However, the role of the upper airway morphology in the pathogenesis and treatment of OSA is still not well known. Cone beam computed tomography (CBCT) is a reliable imaging technique to investigate the upper airway morphology. Therefore, the overall aim of this thesis was to evaluate the roles of the upper airway morphology in the pathogenesis and treatment of different OSA phenotypes (**chapters 2, 3, and 4**) and in the treatment effects of mandibular advancement device (MAD) therapy (**chapters 5 and 6**).

In **Chapter 2**, we aimed to compare the anatomical balance and shape of the upper airway in supine position between adults with positional OSA (POSA) and adults with non-positional OSA (NPOSA). Besides, in **Chapter 3**, we compared the anatomical balance of the upper airway between Dutch and Chinese patients with OSA. The common hypothesis for both chapters was that upper airway morphology is one of the underlying mechanisms between different OSA phenotypes. However, the results indicated that there is no significant difference in the upper airway morphology between POSA and NPOSA groups in the supine position, nor between Dutch and Chinese patients with mild to moderate OSA. Therefore, further investigation involving both anatomical and non-anatomical factors is needed to allow for a better understanding of the difference in the pathogenesis of upper airway collapse between different OSA phenotypes, which is vital to OSA management.

In **Chapter 4**, we aimed to investigate the changes in mandibular position and upper airway dimensions after miniscrew-assisted treatment with premolar extractions in adult patients with Class II high-angle malocclusion. From this study, it can be concluded that by using mini-screws to intrude upper molars, orthodontic premolar extraction treatment results in mandibular counterclockwise rotation and an increase in upper airway dimensions in young adult patients with Class II high-angle malocclusion. As this group of individuals may have a high risk of developing OSA, a longitudinal study is needed to know the long-term influence of the treatment on OSA development.

In **Chapter 5**, we compared the effects of two types of titratable customized MADs, namely MAD-H (allowing limited vertical opening) and MAD-S (allowing free vertical opening), on respiratory parameters and upper airway dimensions in patients with mild to moderate OSA in an RCT with parallel group design. The results indicated that there is no significant difference between the two types of MADs in the effects on respiratory parameters and upper airway dimensions in patients with mild to moderate OSA. Following this study, we further investigated the underlying mechanism of different responses to MAD therapy. In **Chapter 6**, we compared the effects of MAD therapy on upper airway dimensions between responders and non-responders. It was concluded that the changes in the upper airway dimensions induced by MADs are not significantly different between responders and non-responders with mild to moderate OSA. It can be hypothesized that the enlargement of the upper airway is a prerequisite for treatment success, however, the final result is mediated by the non-anatomical factors involved in the pathogenesis of OSA. Future studies on this topic are vital to accurately predict MAD treatment outcome.

Conclusions

The upper airway morphology does not play a significant role in the pathogenesis of different OSA phenotypes and in the treatment effects of MAD. Future research involving both anatomical and non-anatomical factors is needed to better understand the pathogenesis and treatment outcomes of OSA, which is important to realize precision medicine.

Chapter 9

Samenvatting

Obstructieve slaapapneu (OSA) is een veel voorkomende slaap-gerelateerde ademhalingsstoornis, die wordt gekenmerkt door herhaaldelijke volledige of gedeeltelijke obstructies van de bovenste luchtweg die vaak verband houden met zuurstofdesaturaties en ontwakingen. De prevalentie van OSA wordt geschat op 14% bij mannen en 5% bij vrouwen in de algemene volwassen bevolking. OSA wordt in verband gebracht met verschillende ernstige gevolgen voor de gezondheid, zoals cognitieve stoornissen, hart- en vaatziekten en diabetes.

OSA is een heterogene aandoening in zijn pathogenese, met een gecompliceerde interactie van zowel anatomische (bovenste luchtweg) als niet-anatomische factoren. Huidig bewijs ondersteunt dat de vernauwing van de bovenste luchtweg waarschijnlijk de fundamentele pathofysiologische eigenschap van OSA is. De rol van de vorm van de bovenste luchtweg bij de pathogenese en behandeling van OSA is echter nog niet goed bekend. Cone beam computertomografie (CBCT) is een betrouwbare beeldvormingstechniek om de bovenste luchtwegvorm te onderzoeken. Hetalgemene doel van dit proefschrift was het bepalen van de rol van de bovenste luchtwegvorm in de pathogenese en behandeling van verschillende OSA-fenotypes (**Hoofdstukken 2, 3 en 4**) en in de behandelingseffecten van mandibulair repositieapparaat (MRA)-therapie (**Hoofdstuk 5 en 6**).

In **Hoofdstuk 2** is de anatomische balans en vorm van de bovenste luchtweg in rugligging vergeleken tussen volwassenen met positionele OSA (POSA) en volwassenen met niet-positionele OSA (NPOSA). Daarnaast hebben we in **Hoofdstuk 3** de anatomische balans van de bovenste luchtweg tussen Nederlandse en Chinese OSA-patiënten vergeleken. De gemeenschappelijke hypothese voor beide hoofdstukken was dat de vorm van de bovenste luchtweg een van de onderliggende mechanismen is tussen verschillende OSA-fenotypes. De resultaten gaven echter aan dat er geen significant verschil is in de bovenste luchtwegvorm tussen POSA- en NPOSA-groepen in rugligging, noch tussen Nederlandse en Chinese patiënten met lichte tot matige OSA. Daarom is verder onderzoek nodig waarbij zowel anatomische als niet-anatomische factoren betrokken zijn, om meer inzicht te krijgen in het verschil in de pathogenese van de bovenste luchtwegcollapse tussen verschillende OSA-fenotypes, wat van belang is voor de behandeling van OSA.

In **Hoofdstuk 4** wilden we de veranderingen in de stand van de onderkaak en de afmetingen van de bovenste luchtweg onderzoeken na een mini-schroef-geassisteerde orthodontische behandeling met premolarenextracties bij volwassen patiënten met een klasse II malocclusie. Uit deze studie kan worden geconcludeerd dat door het gebruik van mini-schroeven om de bovenmolaren te intruderen, orthodontische premolaarextractiebehandeling resulteert in een mandibulaire

rotatie tegen de klok in, en een toename in de bovenste luchtwegafmetingen bij jongvolwassenen met een klasse II malocclusie. Aangezien deze groep mogelijk een hoog risico heeft om OSA te ontwikkelen, is een longitudinaal onderzoek nodig om het lange termijneffect van deze behandeling op de ontwikkeling van OSA te bepalen.

In **Hoofdstuk 5** vergeleken we de effecten van twee soorten titreerbare, op maat gemaakte MRA's namelijk MRA-H (dat een beperkte verticale opening mogelijk maakt) en MRA-S (dat een vrije verticale opening mogelijk maakt), op ademhalingsparameters en bovenste luchtwegafmetingen bij patiënten met lichte tot matige OSA in een RCT met parallel design. De resultaten gaven aan dat er geen significant verschil is tussen de twee soorten MRA's in de effecten op ademhalingsparameters en bovenste luchtwegafmetingen bij patiënten met lichte tot matige OSA. Na deze studie hebben we het onderliggende mechanisme van verschillende reacties op MRA-therapie verder onderzocht. Daarom hebben we in **Hoofdstuk 6** de effecten van MRA-therapie op de bovenste luchtwegafemtingen vergeleken tussen responders en non-responders. Er werd geconcludeerd dat de door MRA's geïnduceerde veranderingen in de bovenste luchtwegafmetingen niet significant verschillen tussen responders en non-responders. Er kan worden verondersteld dat de vergroting van de bovenste luchtweg een voorwaarde is voor het succes van de behandeling, maar dat het uiteindelijke behandelresultaat wordt gemedieerd door de niet-anatomische factoren die betrokken zijn bij de pathogenese van OSA. Toekomstige studies op dit onderwerp zijn van cruciaal belang om de uitkomst van MRA-behandeling nauwkeurig te kunnen voorspellen.

Conclusies

De morfologie van de bovenste luchtwegen speelt geen significante rol in de pathogenese van verschillende OSA-fenotypen en in de behandelingseffecten van een MRA. Toekomstig onderzoek waarbij zowel anatomische als niet-anatomische factoren betrokken zijn, is nodig om de pathogenese en behandelresultaten van OSA beter te begrijpen, wat van belang is om behandeling op maat te kunnen bieden.

Chapter 10

总结

阻塞性睡眠呼吸暂停综合征(obstructive sleep apnea, OSA)是一种以发生在睡眠时期，由于上气道反复完全或不完全塌陷而导致频繁的呼吸暂停或通气量减低为主要特征的慢性呼吸系统疾病。OSA患者在睡眠过程中常反复发生间歇性低氧和微觉醒。据流行病学研究，OSA的患病率在成年男性中约为14%，女性约为5%。OSA可累及多系统器官并造成多种严重的全身性疾病，例如认知损害、心血管疾病以及糖尿病等。

OSA的发病机制复杂，通常涉及解剖因素（上气道）和非解剖学因素的相互作用。目前的证据表明上气道形态异常是OSA最重要的病理特征之一。然而到目前为止，该因素在OSA的发病机制和治疗机制中的具体作用尚未完全明确。锥形束CT (cone beam computed tomography, CBCT) 是目前研究上气道形态的主要手段之一，可为上气道形态提供可靠的三维的影像学数据。因此，本论文的主要目的是评估上气道形态在不同OSA表型的发病机制以及治疗中的作用（**第2、3和4章**），以及其对下颌前伸矫治器（mandibular advancement device, MAD）疗效的影响（**第5和6章**）。

在**第2章**中，我们将成年OSA患者依据是否存在体位相关性（即仰卧位时OSA加重）进行分组，并比较了体位相关性OSA患者(positional OSA, POSA)和非体位相关性OSA患者（non-positional OSA, NPOSA）在仰卧位时上气道解剖平衡（即舌体面积与上下颌骨框架面积的比值）和上气道形状的差异。此外，在**第3章**中，我们比较了荷兰和中国OSA患者的上气道解剖平衡的差异。在这两个章节中，研究的相似之处在于假设上气道形态的差异是不同OSA表型的内在机制之一。然而，研究结果表明POSA组和NPOSA组在仰卧位时的上气道形态没有显著差异；荷兰和中国轻、中度OSA患者之间的上气道形态也没有显著差异。因此，除解剖因素外，需探索非解剖学因素对不同OSA表型上气道塌陷的发病机制的影响，这利于进一步明确OSA的发病机制并制定OSA的个性化治疗。

在**第4章**中，我们探索了成年高角II类错颌畸形患者在经过支抗钉辅助的前磨牙拔除的正畸治疗后下颌位置和上气道大小变化。结果表明，通过使用支抗钉来压低上颌磨牙，患者的下颌逆时针旋转，且上气道最小横截面积增加。由于高角II类错颌畸形患者相比正常颌患者具有更高的OSA患病风险，该正畸治疗对OSA发病的长期影响需长期纵向研究来继续探索。

在**第5章**中，我们采用了随机平行对照试验比较了两种类型的可调节定制式MAD对轻至中度OSA患者的呼吸参数和上气道大小的影响。两种MAD的主要差别是患者的自由开口度的不同，即MAD-H允许有限开口度，而MAD-S允许自由开口度。结果表明，两种MAD对呼吸参数和上气道大小的影响没有显著差异。在该研究之后，我们进一步探索了MAD治疗成功者和失败者之间的反应机制。因此，在**第6章**中，我们比较了MAD治疗成功者和失败者在MAD治疗过程中上气道大小的变化。结果表明，MAD引起的上气道大小的变化在两组之间没有显著差异。因此，可以进一步

假设上气道的扩大是MAD治疗成功的先决条件，但最终治疗结果由OSA发病机制中的非解剖学因素来调控。未来对这一假设的进一步研究可有助于准确预测MAD治疗结果。

结论

上气道形态在不同OSA表型的发病机制以及在不同MAD的疗效中无显著影响。为实现OSA的精准医疗，未来研究需同时探索解剖学和非解剖学因素对OSA的发病机制和治疗结果的影响。

Appendices

List of publications
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Acknowledgements

List of publications

Shi, X., Sutherland, K., Lobbezoo, F., Berkhout, E., de Lange, J., Cistulli, P., Darendeliler, M., Dalci, O., & Aarab, G. (2023). Upper airway morphology in adults with positional obstructive sleep apnea. Sleep & breathing = Schlaf & Atmung, 10.1007/s11325-023-02879-0. Advance online publication. https://doi.org/10.1007/s11325-023-02879-0

Shi, X., Chen, H., Lobbezoo, F., de Lange, J., van der Stelt, P., Berkhout, E., Guo, J., Ge, S., Li, G., Li, Y., & Aarab, G. (2023). Comparison of the upper airway morphology between Dutch and Chinese adults with obstructive sleep apnea. Sleep & breathing = Schlaf & Atmung, 10.1007/s11325-023-02834-z. Advance online publication. https://doi.org/10.1007/s11325-023-02834-z

Shi, X., Chen, H., Lobbezoo, F., Berkhout, E., de Lange, J., Guo, J., & Aarab, G. (2021). Effects of miniscrew-assisted orthodontic treatment with premolar extractions on upper airway dimensions in adult patients with Class II high-angle malocclusion. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics, 159(6), 724–732. https://doi.org/10.1016/j.ajodo.2020.02.016

Shi, X., Lobbezoo, F., Chen, H., Rosenmöller, B. R. A. M., Berkhout, E., de Lange, J., & Aarab, G. (2023). Comparisons of the effects of two types of titratable mandibular advancement devices on respiratory parameters and upper airway dimensions in patients with obstructive sleep apnea: a randomized controlled trial. Clinical oral investigations, 27(5), 2013–2025. https://doi.org/10.1007/s00784-023-04945-z

Shi, X., Lobbezoo, F., Chen, H., Rosenmöller, B. R. A. M., Berkhout, E., de Lange, J., & Aarab, G. (2023). Effects of mandibular advancement devices on upper airway dimensions in obstructive sleep apnea: responders versus non-responders. Clinical oral investigations, 27(9), 5649–5660. https://doi.org/10.1007/s00784-023-05186-w

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Chapter 2: Upper airway morphology in adults with positional obstructive sleep apnea

X. Shi, K. Sutherland, F. Lobbezoo, E. Berkhout, J. de Lange, P.A. Cistulli, M.A. Darendeliler, O. Dalci, & G. Aarab

Study conceptualization and design	XS, KS, GA
Data collection	XS
Data analysis and interpretation	XS, KS, GA
Manuscript original draft	XS
Manuscript editing and review	XS, KS, FL, EB, JdL, PC, MD, OD, GA

Chapter 3: Comparison of the upper airway morphology between Dutch and Chinese adults with obstructive sleep apnea

X. Shi, H. Chen, F. Lobbezoo, J. de Lange, P. van der Stelt, E. Berkhout, J. Guo, S. Ge, G. Li, Y. Li, & G. Aarab

Study conceptualization and design	XS, HC, GA
Data collection	XS, HC
Data analysis and interpretation	XS, HC
Manuscript original draft	XS, HC
Manuscript editing and review	XS, HC, FL, JdL, PvdS, EB, JG, SG, GL, YL, GA

Chapter 4: Effects of miniscrew-assisted orthodontic treatment with premolar extractions on upper airway dimensions in adult patients with Class II high-angle malocclusion

X. Shi, H. Chen, F. Lobbezoo, E. Berkhout, J. de Lange, J. Guo, & G. Aarab

Study conceptualization and design	XS, JG, GA
Data collection	XS
Data analysis and interpretation	XS, HC, GA
Manuscript original draft	XS
Manuscript editing and review	XS, HC, FL, EB, JdL, JG, GA

Chapter 5: Comparisons of the effects of two types of titratable mandibular advancement devices on respiratory parameters and upper airway dimensions in patients with obstructive sleep apnea: a randomized controlled trial

X. Shi, F. Lobbezoo, H. Chen, B. R. A. M. Rosenmöller, E. Berkhout, J. de Lange, & G. Aarab

Study conceptualization and design	XS, GA
Data collection	XS, HC
Data analysis and interpretation	XS, GA
Manuscript original draft	XS
Manuscript editing and review	XS, FL, HC, BR, EB, JdL, GA

Chapter 6: Effects of mandibular advancement devices on upper airway dimensions in obstructive sleep apnea: responders versus non-responders

X. Shi, F. Lobbezoo, H. Chen, B. R. A. M. Rosenmöller, E. Berkhout, J. de Lange, & G. Aarab

Study conceptualization and design	XS, GA
Data collection	XS, HC
Data analysis and interpretation	XS, GA
Manuscript original draft	XS
Manuscript editing and review	XS, FL, HC, BR, EB, JdL, GA

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Xiaoxin Shi was born on 20th March 1990 in Laiyang, Shandong, China. She completed her primary school and high school education in her hometown. In 2008, she enrolled in Shandong University to pursue her bachelor studies in the field of stomatology. After obtaining her bachelor's degree in 2013, she continued her academic journey by pursuing a master's degree at Shandong University, specializing in Orthodontics. Alongside her clinical work, she devoted her research efforts to investigating the effect of orthodontic treatments on upper airway dimensions. Following the completion of her master's degree in 2016, she embarked on a Ph.D. program at the Academic Centre for Dentistry Amsterdam (ACTA). During her Ph.D. studies, her research interests focused on exploring the role of upper airway morphology in the pathogenesis and treatment of obstructive sleep apnea.

Acknowledgements

Completing my Ph.D. journey has been a challenging endeavor, and I am deeply grateful for the support and assistance I received from numerous individuals. Without your help, this thesis would not have been possible. As I come to the end of this journey, I would like to express my sincere gratitude and appreciation to all those who have contributed to my success.

Supervisors:
First and foremost, I would like to express my deepest appreciation to my research supervisors. Their immense knowledge, invaluable advice, continuous support, and patience have encouraged me in all the time of my academic research.

Dear prof. dr. G. Aarab, dear Ghizlane, I cannot fail to express my deepest gratitude to you. Looking back, I realize how naïve I was when I came to the research field of OSA. Undoubtedly, I must have made many silly mistakes during my research journey. However, you have always been there to aid and support, rather than placing blame. Whenever I have faced difficulties and felt that the end of the road was near, you have consistently encouraged me to persevere. In moments of journal rejections, you have always been the first to offer encouragement. Your profound knowledge and invaluable insights into science have been a continuous source of inspiration for me, and they have completely improved my understanding of research and science. I am truly grateful for the opportunity to work with you.

Dear prof. dr. F. Lobbezoo, dear Frank, I would like to express my deepest appreciation for the invaluable help and guidance you have provided to me. Your wisdom in handling various issues and your ability to offer timely and insightful advice have been instrumental in my growth. Besides, I am particularly grateful for the meticulous editorial revisions you have made to my manuscripts. Your thoroughness never fails to impress me, and I greatly appreciate the care and precision you put into refining my work. Your continuous contributions and breakthroughs in your research areas has motivated me to persevere and explore in science.

Dear dr. W.E.R. Berkhout, dear Erwin, I would also like to express my heartfelt appreciation for the resources, office space, and technical support you have provided for my project. Your expertise in imaging analysis has been invaluable in improving the quality of my manuscripts. In addition to imaging technique, I must commend your exceptional skills in internet connectivity. You helped me to safely save images for international collaboration projects and helped me to access

ACTA from home during the early stages of the COVID-19 pandemic, ensuring the continuity and effectiveness of my research.

Dear Prof. dr. J. de Lange, dear Jan, I would like to express my utmost gratitude to you for providing the topic and subjects for my Ph.D. project. You have provided the necessary support and assurance to ensure the progress of the project. Besides, I am sincerely appreciative of the positive feedback you have given on my work, which has encouraged and supported me.

Co-authors:
Dear dr. H. Chen, dear Hui, I would also like to extend my deepest appreciation for your assistance in reviewing my articles. Your efficient work and practical suggestions have been invaluable. Your enthusiasm for science has been truly inspiring, and I hope to emulate that enthusiasm in my own work. Besides, your timely updates as the corresponding author have been reliable and greatly appreciated.

Dear B.R.A.M. Rosenmöller, dear Boudewijn, a lot of thanks for your help in collecting scattered patient data. Your prompt responses to my requests and the provision of hard-to-find research materials have been immensely helpful. I am also grateful for your generous sharing your recent research outcomes with me.

Dear dr. K. Sutherland, dear Kate, I sincerely thank you for providing me with the opportunity to collaborate with your team. Your patient and kind responses to my emails have facilitated smooth collaboration. I greatly appreciate your offer to assist in rewriting the manuscript when it exceeded the journal's word limit. Your accomplishments in the field of obstructive sleep apnea are truly admirable.

Dear prof. dr. J. Guo, dear Jing, I am deeply grateful for your guidance during my three-year master's program. Our time spent together in the clinic allowed me to acquire invaluable orthodontic knowledge and skills and gave me the joy of being a dentist. You also guided me in writing my first journal article, which paved the way for my future in the scientific world. In addition, your care and support extended beyond the academic realm, bringing me warmth and comfort throughout the years.

Dear prof. dr. P. van der Stelt, dear Paul, thank you very much for helping to establish the research connection between me and ACTA in the early stages. Your assistance in refining my research questions and your support in my personal life, including helping me move from Deventer to Amsterdam, hosting us at Chinese festivals, and numerous other acts of kindness, are deeply appreciated.

I also would like to thank the colleagues from the University of Sydney, Australia: Prof. dr. M.A. Darendeliler, Dr. O. Dalci, Prof. dr. P.A. Cistulli; and from Shandong University, China: Prof. dr. S. Ge, Prof. dr. G. Li, and Prof. dr. Y. Li. Thank you all for your contributions in facilitating our overseas collaborations. I am grateful for your assistance and revisions to the manuscripts.

Paranymphs:
Dear M. Reyes Sevilla and dr. J. Jin, dear Marisol and Jianfeng, I want to express my sincere gratitude to you for being my paranymphs. Your assistance in sending emails, gathering information, distributing the thesis, and providing support during the final phase of my defense has been invaluable. Your help truly eased my burden and made a significant difference. Thank you.

Colleagues:
Dear dr. N. Su, dear Naichuan, thank you for your valuable suggestions regarding my statistical problems. Your guidance always steered me in the right direction and helped me overcome challenges.

Dear prof. dr. Y. Liu, dear Maria, thank you for your support since I began working at ACTA. I deeply appreciate your kindness and caring towards Chinese students. You also frequently check whether I am doing okay with my research, which made me feel cared for and supported.

Dear N. Sehar, dear Nafit, thank you for assisting me in taking care of the CBCT machine. In addition, thank you for the time that we had lunches together and for being the first colleague at ACTA whom I got to know and talk with. You helped me become more acquainted with ACTA and the Netherlands.

Dear H. van Echteld, dear Heleen, thank you for your support in obtaining office supplies, arranging access to ACTA, and making appointments for me. Besides, thank you for helping me find a suitable family doctor nearby.

Dear P.D. Gilhuys, dear Patricia, thank you for your assistance in scheduling various appointments for me.

Dear dr. J.A.M. Korfage, dear Hans, thank you for your help in checking article similarities.

Dear dr. H.S. Brand, dear Henk, thank you for your help in checking the availability of a chairman for my defense and checking my ECTs.

Friends:
I would like to express my gratitude to my friends in the Netherlands: Ning Zhou, Zhengfei Huang, Jiayu Li, Boyuan Kuang, Thiprawee Chattrattrai, Dingyang Li, and Deshui Li. Thank you for the time we spent together and the relaxing, inspiring, and encouraging conversations we had.

I would also like to thank my dear friend Xiaoyan Wang. Our friendship, which began at Shandong University, has continued in the Netherlands, which is truly remarkable. Thank you for the thoughts, joys, and understandings we've shared over the years. I will always cherish our friendship.

Family:
感谢我的父母，感谢你们给予我的一切，家人永远是最温暖的港湾。同时，我也要感谢我的伴侣陈昭，我们始终相互支持、互相鼓励来面对生活中的挑战，愿我们能够继续砥砺前行。