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CLINICAL REVIEW

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

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SUMMARY

Mandibular advancement device (MAD) therapy is the most commonly used second-line treatment for obstructive sleep apnea (OSA), but MAD may be ineffective in a subgroup of patients. The aim of this systematic review is to identify predictors of the efficacy of oral appliance (OA) therapy for OSA in adult patients. This review focuses on performing the quantitative analysis by subgroups based on the response criteria used in the literature and based on the type of device. PubMed, EMBASE, Scopus, Web of Science and Cochrane databases was conducted to identify potentially relevant studies published until Dec 2021. The search identified 1343 preliminary references. A total of 99 studies met the eligibility criteria and were included in the review, and 60 in the meta-analysis. The quality of studies was assessed using the Newcastle–Ottawa scale and the Cochrane scale. Based on meta-analysis, and considering a low to moderate evidence profile according to the GRADE scale, responders are younger patients, with smaller neck circumference, lower body mass index. Responders have shorter maxillary length, lower anterior and posterior facial height, a shorter distance from the hyoid bone to the third cervical vertebra, a shorter airway length, a smaller minimum airway cross-sectional area and a higher minimum oxygen saturation during sleep. Responders needed a lower optimal continuous positive airway pressure than non-responders. The type of device has not affected the results of the meta-analysis. The criterion "AHI <10 and reduction AHI >50%" is the one that provides the "weight" of significance for several variables. This criterion should be taken into consideration for future studies to predict OSA treatment by OA.

Introduction

Obstructive sleep apnea syndrome (OSA) is a common disorder characterized by repeated collapse of the upper airway during sleep, resulting in the suspension of airflow. The need to regain airway patency and normal breathing produces arousals and thus, sleep fragmentation [1].

The diagnosis of this pathology is confirmed after performing a nocturnal polysomnography (PSG) or home sleep test [2]. Through this sleep study, the severity of the respiratory disorder is determined, which is generally expressed by means of the apnea–hypopnea index (AHI), i.e., the average number of apneas and hypopneas per hour of sleep. It can be classified as mild (AHI 5–15), moderate (AHI 15–30) or severe (AHI > 30) [2]. In 2015, Heinzer et al. identified a prevalence of OSA, defined by an apnea–hypopnea index (AHI) greater than five events per hour, of approximately 49% in men aged 40 to 85 and 24% in women within

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Abbreviations

AHI	apnea–hypopnea index
ANB	A point-nasion-B point
BMI	body mass index
CBCT	cone beam computed tomography
CPAP	continuous positive airway pressure
CSAmin	minimum airway cross-sectional area
DISE	drug-induced sleep endoscopy
EMBASE	excerpta medica database
ESS	Epworth sleepiness scale
MAD	mandibular advancement device
$MinSaO_2$	minimum oxygen saturation
MP	mandibular plane
OA	oral appliance
ODI	oxygen desaturation index
OSA	obstructive sleep apnea
PALM	pcrit, arousal threshold, loop gain and muscle responsiveness
Pcrit	passive critical closing pressure of the upper airway
PICO	patient/population, intervention, comparison, outcome
PRISMA	preferred reporting items for systematic reviews and meta-analysis
PROSPERO	international prospective register of systematic reviews
PSG	polysomnography
SN	sella-nasion
SNA	sella-nasion-A point
SNB	sella-nasion-B point

the same age range [3]. Benjafield et al. described a global prevalence of almost one billion people affected [4].

OSA has serious repercussions since it can cause daytime sleepiness and neurocognitive disorders triggered by the sleep fragmentation present in these patients. In addition, it is associated with an increased risk of cardiometabolic morbidity, such as hypertension, myocardial infarction, stroke, heart failure and insulin resistance, and thus indirectly contributes to increased mortality. In fact, the recent data of the study of Lisan et al. lend support for accelerated vascular aging in individuals with high risk of OSA [5,6].

Although OSA increases the risk of all-cause and cardiovascular mortality, this condition is often underrecognized and undertreated in cardiovascular practice. For this, the American Heart Association recommend screening for OSA in patients with resistant/poorly controlled hypertension, pulmonary hypertension, and recurrent atrial fibrillation after either cardioversion or ablation [7].

Treatment options range from conservative measures, such as weight loss and continuous positive airway pressure (CPAP), to more invasive treatments such as soft tissue surgery like uvulopalatopharyngoplasty (UPPP) or maxillomandibular surgery [1,2]. There is a relation between the severity of OSA disease and cardiovascular risk, but effective treatment with nasal CPAP significantly reduces the cardiovascular outcomes associated with this medical condition [5]. However, considerable patient noncompliance rates represent a major limitation to widespread implementation of this treatment option, and even good compliant patients at the beginning tend to abandon the therapy in the long term, mainly mild to moderate cases [1,8].

Currently, mandibular advancement devices (MAD) are recommended by the American Academy of Sleep Medicine (AASM) as first-line treatment in mild and moderate OSA in patients without severe cardiovascular comorbidity and in severe OSA when CPAP treatment fails or is refused [1]. Although oral devices have less impact on reducing AHI, both treatments have shown to have a similar impact on clinical outcomes, including symptomatology and cardiovascular outcomes [9]. The meta-analysis of Pengo et al. included 68 randomized controlled trials that compared CPAP or MADs to reduce cardiovascular risk. Overall, both the CPAP and MADs were associated with blood pressure reduction [10]. In addition, MAD is a treatment better tolerated by patients, resulting in higher patient compliance, and therefore similar efficacy in the clinical practice [9].

Their mechanism of action consists in maintaining the patency of the upper airway avoiding collapse. They act by correcting the anatomical imbalance of patients with OSA, specifically by stabilizing and increasing the velopharyngeal airway space, reducing its collapsibility [1].

The efficacy of MADs is less than that of CPAP, but oral appliances have similar effectiveness, with a self-reported compliance rate of approximately 80%, and typically are preferred over CPAP [11]. However, the treatment effectiveness of this pathology by means of MAD is limited by the interindividual variability of treatment results and the lack of information on the correct selection of suitable patients. In fact, oral devices are an effective treatment for 60–70% of patients [1]. Therefore, accurate patient selection is essential to optimize treatment outcomes using MAD and thus avoiding unnecessary costs. This justifies the need to identify phenotypes prone to predict response to treatment with MAD.

Considering the heterogeneity of the efficacy of oral devices, the main objective of this review is to unify the available data that focus on identifying subgroups of OSA patients who have superior treatment efficacy (responders) compared to other patients whose efficacy is lower (non-responders).

The present systematic review and meta-analysis focuses on advancing in the knowledge for a more precise sleep medicine in the future. Since there are several criteria for responders based on the AHI described in the literature, one objective of this review is to perform a quantitative analysis by subgroups to reduce the heterogeneity of the results. Another objective of the present review is to carry out a quantitative analysis according to the type of device used.

Material and methods

The following systematic review was performed following the guidelines of the 2020 PRISMA (preferred reporting items for systematic reviews and meta-analysis) guideline update [12].

PICO question

The objective was to answer the following PICO (population/patient, intervention, comparison, outcome) question: What are the predictors of success in the treatment of adult patients with sleep apnea using mandibular advancement devices?

Inclusion and exclusion criteria

“Articles” and “Articles in press” were included in the study: randomized clinical trials, longitudinal studies, retrospective and prospective cohort or case–control studies. No restrictions were

applied regarding year of publication or language. Inclusion criteria applied included: 1) studies that have diagnosed adults with OSA with a PSG who are prescribed a MAD; 2) studies that have evaluated treatment response using a second PSG; 3) studies that have evaluated the baseline phenotypic characteristics of treatment responders. Studies with a sample size of less than 12 patients were excluded.

Search strategy

A comprehensive electronic search of the Medline (PubMed), Excerpta medica database (EMBASE), Scopus, Web of science, and Cochrane databases was conducted to identify potentially relevant studies regardless of language. An electronic search of gray literature was performed through Opengrey. In particular cases, the authors of the articles were contacted via e-mail to request any necessary information. The references of the included studies were hand-searched to identify any articles that might meet the inclusion criteria and that were not found in the databases. The search was updated in December 2021.

Search terms

The search strategy included the main terms “obstructive sleep apnea”, “snoring”, “sleep-related breathing disorder”, “mandibular advancement device”, “oral appliance”, “predict”, “prediction”, “compare”, “comparison”, “physiologic predictors”, “anatomical balance”, “customized OSA therapy” and “phenotypic”. Boolean operators (“OR” and “AND”) were used to link terms related to the research question.

These keywords were divided into three groups and an exhaustive search of all possible combinations between the terms in the three groups was performed. The identified articles were exported to Mendeley desktop 1.13.3 software (Mendeley Ltd, London, England) to search for duplicates. The search strategy for all databases is given in complementary material (Table S1).

Selection process

Two reviewers (SC-G and RM-P), working independently, systematically evaluated the titles and abstracts of all identified articles. In case of disagreement, a third reviewer (MG-S) was consulted. In the event that the abstract did not contain sufficient information to make a decision, the reviewers read the full-text article before making a final decision. In the second phase of the study selection, the same reviewers read the full-text articles and the reasons for rejection of excluded articles according to the inclusion and exclusion criteria were recorded.

Study data

The following main variables were recorded for each article: author and year of publication, type of study, country and population studied, reference guide, sample size, demographic variables (sex and age), severity of OSA, type of device used, definition of responders (cut-off AHI value) and method of assessment (two-dimensional, three-dimensional, nasopharyngoscopy, volume flow curve, videofluoroscopy, etc.).

The main variables recorded were grouped into clinical variables (sex, age, body mass index (BMI), race, neck circumference, Epworth sleepiness scale (ESS)); anatomical variables, both physiological (location and characteristics of airway collapse, nasal obstruction, Mallampati scale grade) and craniofacial (see Fig. 1), and soft tissue; non-anatomical variables (passive critical closing pressure of the upper airway (Pcrit) or pharyngeal collapsibility, awakening threshold, respiratory control stability or loop gain, muscle response); polysomnographic variables (AHI, arousals index, minimum oxygen saturation ($minSaO_2$.), oxygen desaturation index (ODI 4%), sleep efficiency, AHI supine/non-supine position, AHI REM/NREM sleep stage, AHI predominant apneas/hypopneas) and treatment variables (optimal CPAP pressure and therapeutic mandibular advancement).

Quality assessment

The quality of the studies was assessed by the same investigators, working independently, using the Newcastle−Ottawa scale to evaluate observational studies and the Cochrane scale for randomized clinical trials [13]. Any discrepancies between the two investigators were resolved by consensus, and a third investigator was consulted in case of doubt. The GRADE tool for formulating and grading recommendations in clinical practice have been used.

Measurement of variables and results synthesis (effect measures)

Means and initial and final confidence intervals were recorded for clinical variables (BMI, age, gender, neck circumference and ESS), polysomnographic variables (baseline AHI, arousal index and $minSaO_2$), anatomical cephalometric variables (mandibular length, maxillary length, SNA, SNB, ANB, mandibular position relative to the cranial base (SN-MP), anterior facial height, posterior facial height, protrusion, overbite, gonial angle, hyoid to mandibular plane distance, hyoid to third cervical vertebra distance and hyoid to retrognation point distance), soft tissue anatomical variables through cone beam computed tomography (CBCT) (soft palate width and length, tongue length), physiological anatomical variables (airway volume, airway length, minimum airway cross-sectional area (CSAmin), upper airway space and lower airway space) and treatment variables (optimal CPAP pressure).

Synthesis methods

A meta-analysis was performed for each of the variables analyzed, and the studies were combined using the random-effects method (inverse-variance method). The design of the meta-analysis was carried out by subgroups, regarding the type of device used (monoblock or adjustable biblock) and the criterion of responders used.

The effect size was estimated using a mean difference between responders and non-responders and between subgroups. The Z test was used to assess significance for a $p < 0.05$. Heterogeneity was assessed using the Q test, the p-value of the Q test, and the I^2. The prediction interval has been used to obtain general prediction results of the analyzed parameters.

Results

Study selection and flowchart

The search identified 1343 preliminary references related to predictors of response to sleep apnea treatment with mandibular advancement devices, of which 243 were found in PubMed, 364 in EMBASE, 396 in Web of science, 315 in Scopus, 25 in Cochrane, 15 in registers. After excluding the 462 duplicated articles, the remaining 896 were examined. Of these, 787 were excluded by reading the title and abstract, as they were not related to the research question. After reading the full text of the resulting 109 articles, 10 were excluded (Table S2). Finally, 99 articles met the eligibility criteria and were included in the qualitative review, and

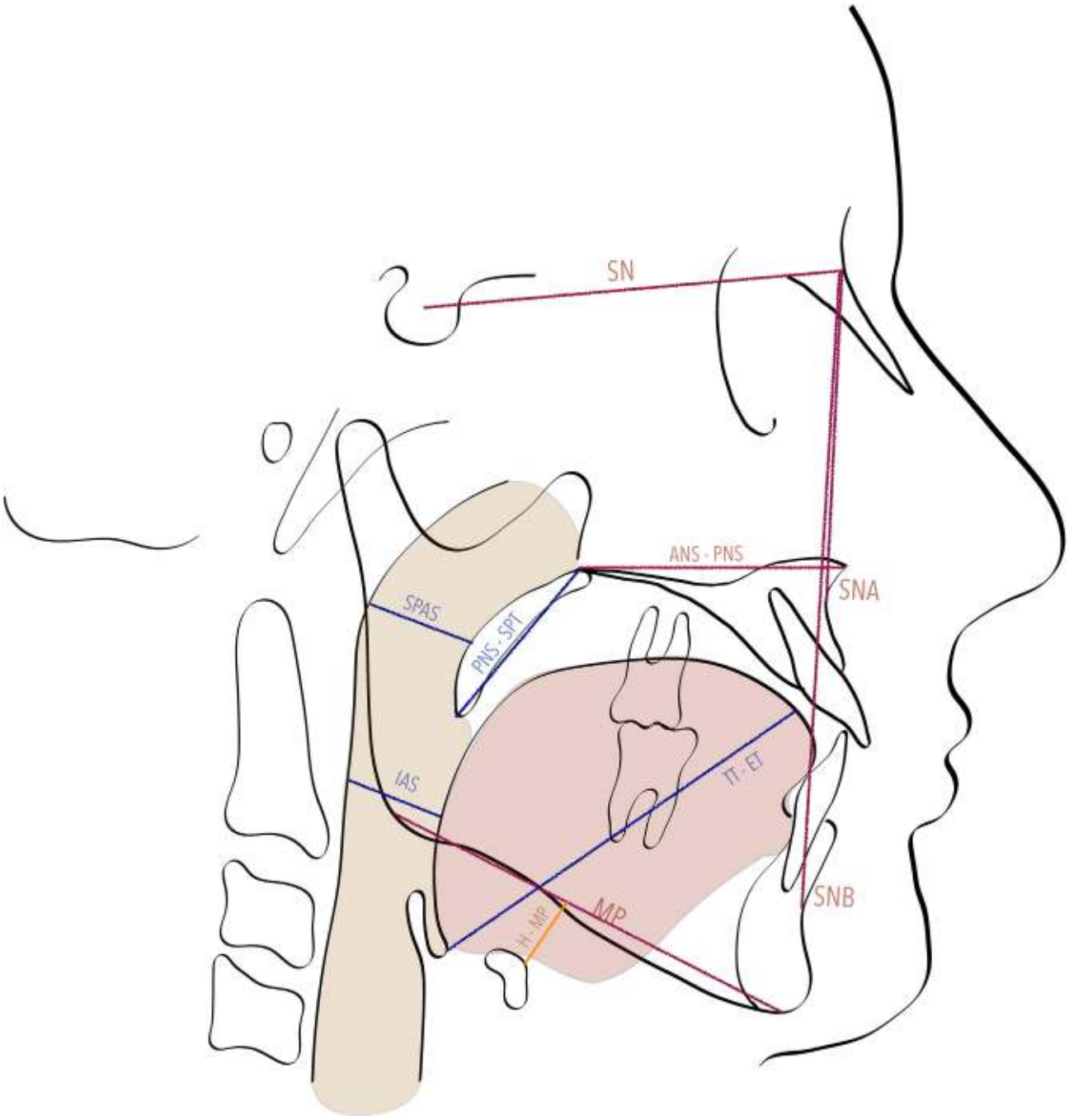

Fig. 1. Cephalometric measurements. Abbreviations: ANS = anterior nasal spine; H = hyoid bone; IAS = lower airway; MP = mandibular plane (gonion-menton); PNS = posterior nasal spine; SN = sella-nasion; SNA: sella-nasion-A point; SNB: sella-nasion-B point; SPAS = upper airway; SPT = soft palate tip.

60 were included in the quantitative review (meta-analysis). The PRISMA flowchart provides an overview of the article selection process (see Fig. 2).

Fig. 2 represents the flowchart from the 2020 PRISMA guideline update, which includes a new scheme for updated systematic reviews [12]. Since there is a systematic review with the same PICO question published by Chen H et al. in 2020 and updated in 2019 that include 42 articles, we updated the search as there were 57 more articles that met the inclusion criteria, enough to modify the existing results of the systematic review and meta-analysis described by Chen H et al. [14]. The search strategies of both reviews differ as a larger number of search terms have been used (see Table S1). Finally, all 99 articles were included in the present systematic review.

Characteristics of the included studies

The characteristics of the 99 studies included in the systematic review are summarized in complementary material (Table S3). Of these, three were randomized clinical trials [15–17] (87 patients included) and 95 were observational studies [18–113]. Of the 96 observational studies (93 cohort studies that included 8403 patients and three case–control studies that included 270 patients), 57 were prospective in design while 39 were retrospective in

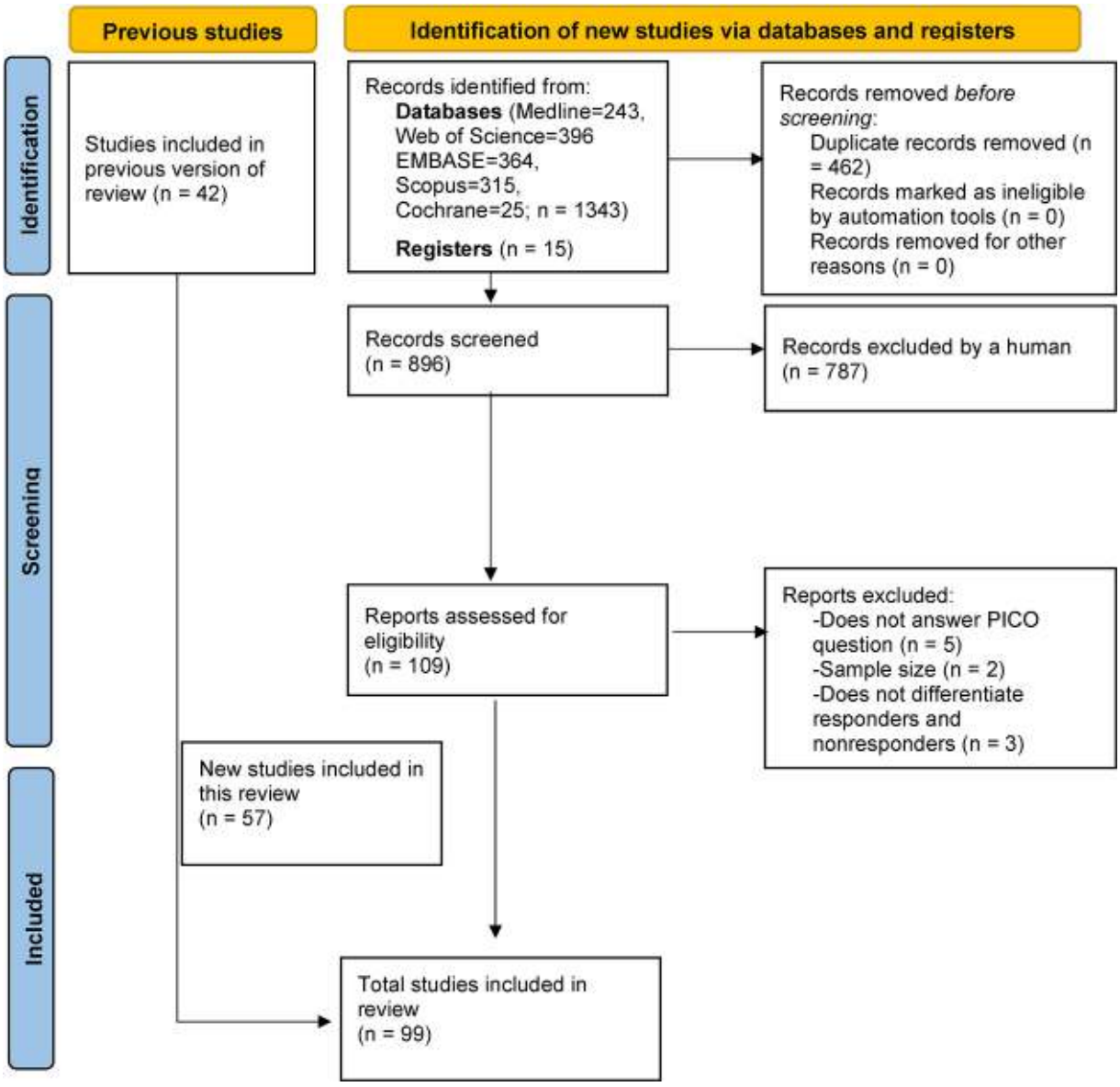

Fig. 2. PRISMA 2020 flow diagram for updated systematic reviews.

design, with only one follow-up point in time to assess treatment effectiveness.

Most of the articles presented high quality on the Newcastle–Ottawa scale (Table S4, Table S5, Fig. S1, Fig. S2). On the Cochrane scale (Table S6 and Fig. S3) all three articles presented quality, with a low risk of bias in minimum five of the seven items.

Definition of response to treatment

The primary variable for defining responders was AHI. There is a large variability in the definition of responders to OA treatment described in the literature. However, the main criteria have been grouped to homogenize the results of the meta-analysis, as the reduction of AHI below a specific value (criterion 1: AHI <10) [18,23,25,29,44,55,67,69,70], or by percentage reduction of AHI from baseline (criterion 2: AHI reduction >50%) [21,22,31–33,73–81]. Or a combination of both (criterion 3) [15,25–28,42,43,92–97].

Type of device used and device adjustment

Regarding the design of the mandibular advancement device, most studies used a custom-made adjustable two-piece device [20,21,26,28–30], while others used a custom-made monoblock device [46,49,51,52].

Quantitative synthesis

The main differences between both groups are described in Table 1. In relation to clinical variables, responders are younger patients, with smaller neck circumference and lower body mass index (see Fig. 3). The mean BMI of 3775 patients was included in the meta-analysis. Mean BMI of non-responders is 28.55 ± 4.41 kg/m^2 and is 1.57 kg/m^2 lower in responders (95% CI: −2.21; −0.92; $p < 0.0001$; GRADE tool: low evidence profile). The age of 3722 patients was analyzed. The mean of non-responders is 51.67 ± 10.2 y and responders are 3.55 y younger than non-responders (95% CI: −4.43; −2.67; $p < 0.0001$; prediction

Table 1
Meta-analysis of study variables.

Variables	N Studies (K)	N Resp	N Non Resp	Mean difference (IC 95%)	Z value	P value	I^2
Clinical variables							
Body mass index*	45	2062	1713	**−1.57 (−2.21; −0.92)**	−4.74	**<0.0001***	82%
Age*	44	2022	1700	**−3.55 (−4.43; −2.67)**	−7.86	**<0.0001***	34%
Gender (males)	36	2222	1595	0.81 (0.58; 1.13)	−1.25	0.2112	68%
Neck circumference (cm)*	19	1328	937	**−1.16 (−1.54; −0.79)**	−6.08	**<0.0001***	46%
Epworth sleepiness scale	12	537	469	0.56 (−1.23; 2.35)	0.61	0.5394	86%
Cephalometric variables							
Mandibular length (mm)	4	73	54	0.54 (−2.96; 4.03)	0.30	0.763	72%
Maxillary length (mm)*	4	147	77	**−0.69 (−1.37; −0.01)**	−1.98	**0.047***	0%
SNA (°)	14	451	266	−0.93 (2.99; 1.13)	−0.89	0.374	96%
SNB (°)	15	416	294	−0.60 (−1.96; 0.76)	−0.87	0.385	90%
ANB	11	297	187	−0.27 (−0.93; 0.19)	−1.29	0.196	63%
SN-MP	8	196	128	0.35 (−1.29; 1.99)	0.42	0.674	39%
Anterior facial height (mm)*	6	198	114	**−2.86 (−4.25; −1.46)**	−4.01	**<0.0001***	18%
Posterior facial height (mm)*	6	184	101	**−2.31 (−3.18; −1.45)**	−5.26	**<0.0001***	0%
Overbite (mm)	8	387	187	0.26 (−0.32; 0.84)	0.88	0.377	48%
Overjet (mm)	9	428	232	0.30 (−0.27; 0.87)	1.03	0.304	57%
Gonial angle	6	192	99	0.30 (−0.13; 0.74)	1.37	0.170	0%
Hyoid bone-MP (mm)	10	268	154	−1.18 (−3.41; 1.06)	−1.03	0.302	86%
3rd cervical − hyoid* (mm)	7	164	91	**−0.94 (−1.45; −0.44)**	−3.67	**0.0002***	4%
Retrognation-hyoid (mm)	3	80	43	−1.54 (−5.18; 2.10)	−0.83	0.406	52%
Soft tissues variables							
Length of soft palate (mm)	14	451	266	−0.93 (−2.99; 1.13)	−0.89	0.374	96%
Width of soft palate (mm)	6	203	124	−0.05 (−1.06; 0.96)	−0.10	0.923	68%
Length of tongue (mm)	4	100	63	−0.82 (−2.93; 1.30)	−0.75	0.450	0%
Physiological variables							
Upper airway volume (cm^3)	3	119	83	−0.38 (−1.94; 1.17)	−0.48	0.629	69%
Upper airway length (mm)*	5	150	115	**−1.02 (−1.82; −0.21)**	−2.47	**0.0136***	0%
CSAmin (mm^2)*	3	117	88	**−9.14 (−12.80; −5.48)**	−4.89	**<0.0001***	0%
Superior airway space (mm)	13	384	221	−0.93 (−1.95; 0.10)	−1.78	0.0755	70%
Inferior airway space (mm)	14	445	264	−0.83 (−1.72; 0.06)	−1.83	0.0671	52%
Polysomnographic variables							
AHI (events/h)	41	2269	1732	−5.91 (−13.12; 1.30)	−1.61	0.1083	99%
$MinSaO_2$ (%)*	15	500	368	**1.46 (0.21; 2.70)**	2.30	**0.0215***	67%
Arousal index	7	162	138	−2.57 (−6.69; 1.55)	−1.22	0.2209	64%
Treatment variables							
Optimal CPAP pressure*	5	146	170	**−1.25 (−1.94; −0.55)**	−3.51	**0.0004***	37%

*p < 0.05. Abbreviations. AHI: apnea–hypopnea index; ANB: Point A-Nasion-Point B; CSAmin: minimum airway cross-sectional area; CPAP: continuous positive airway pressure; I^2: heterogeneity; $MinSaO_2$: minimum oxygen saturation; SNA: sella-nasion-point A; SNB: sella-nasion-point B; SN-MP: sella-nasion-mandibular plane.

interval −6.75; −0.35; GRADE tool: moderate evidence profile). The neck circumference of 2265 patients was included in the quantitative analysis. The mean of non-responders is 40.45 ± 3.05 cm and is 1.16 cm smaller in responders than in non-responders (95% CI: −1.54; −0.79; p < 0.0001; prediction interval −2.32; −0.02; GRADE tool: moderate evidence profile). No significant differences were found in baseline ESS scores between responders and non-responders (p = 0.5394). No significant differences were found either in the sex of both groups (p = 2112) (Table 1).

In relation to the cephalometric anatomical variables, the responders have shorter maxillary length (224 patients included; GRADE tool: low evidence profile), lower anterior and posterior facial height (312 and 285 patients included respectively; GRADE tool: moderate evidence profile) and a shorter distance from the hyoid bone to the third cervical vertebra (255 patients included; GRADE tool: moderate evidence profile). The mean maxillary length of non-responders is 70.18 ± 3.03 mm and the length of responders is 0.69 mm shorter than that of non-responders (95% CI: −1.37; −0.01; p < 0.05). The mean anterior facial height of non-responders is 115.66 ± 6.11 mm and the height of responders is 2.86 mm shorter than that of non-responders (95% CI: −4.25; −1.46; p < 0.0001). The mean posterior facial height of non-responders is 77.92 ± 4.89 and the height of responders is 2.31 mm shorter than that of non-responders (95% CI: −3.18; −1.45; p < 0.0001; prediction interval −3.54; −1.09). The mean distance from the hyoid bone to the third cervical vertebra of non-responders is 34.96 ± 3.94 mm and it is 0.94 mm shorter in responders than in non-responders (95% CI: −1.45; −0.44; p = 0.0002; prediction interval −1.73; −0.16) (see Fig. 4).

No variable related to soft tissues has shown statistical significance in the meta-analysis (Table 1).

Regarding physiological anatomical characteristics, the mean of minimum airway cross-sectional area in non-responders is 50.6 ± 21.3 mm^2 and it is 9.14 mm^2 smaller in responders (95% CI: −12.80; −5.48; p < 0.0001; GRADE tool: low evidence profile). On the other hand, the mean of airway length of non-responders is 77.95 ± 6.06 mm and the length in responders is 1.02 mm shorter than that of non-responders (95% CI: −1.82; −0.21; p < 0.05; GRADE tool: moderate evidence profile).

No significant differences were found between both groups in terms of upper (p = 0.0755) and lower (p = 0.0671) airway space, nor in airway volume (p = 0.629).

Regarding polysomnographic variables, the mean percentage of $minSaO_2$ of non-responders is 82.08 ± 6.1 and responders have a higher percentage of oxygen saturation during sleep, it is specifically 1.46 points higher than non-responders (95% CI: 0.21; 2.70; p < 0.05; GRADE tool: low evidence profile). The mean of AHI in responders is 26.14 ± 11.38 events/h and in non-responders is 32.06 ± 14.64 events/h. However, this parameter has not obtained significant differences in the results of the meta-analysis (p = 0.1083).

Finally, it has been obtained that responders to treatment with oral devices needed a lower optimal CPAP pressure (specifically 1.25 cmH_2O less) than non-responders, and the mean of non-

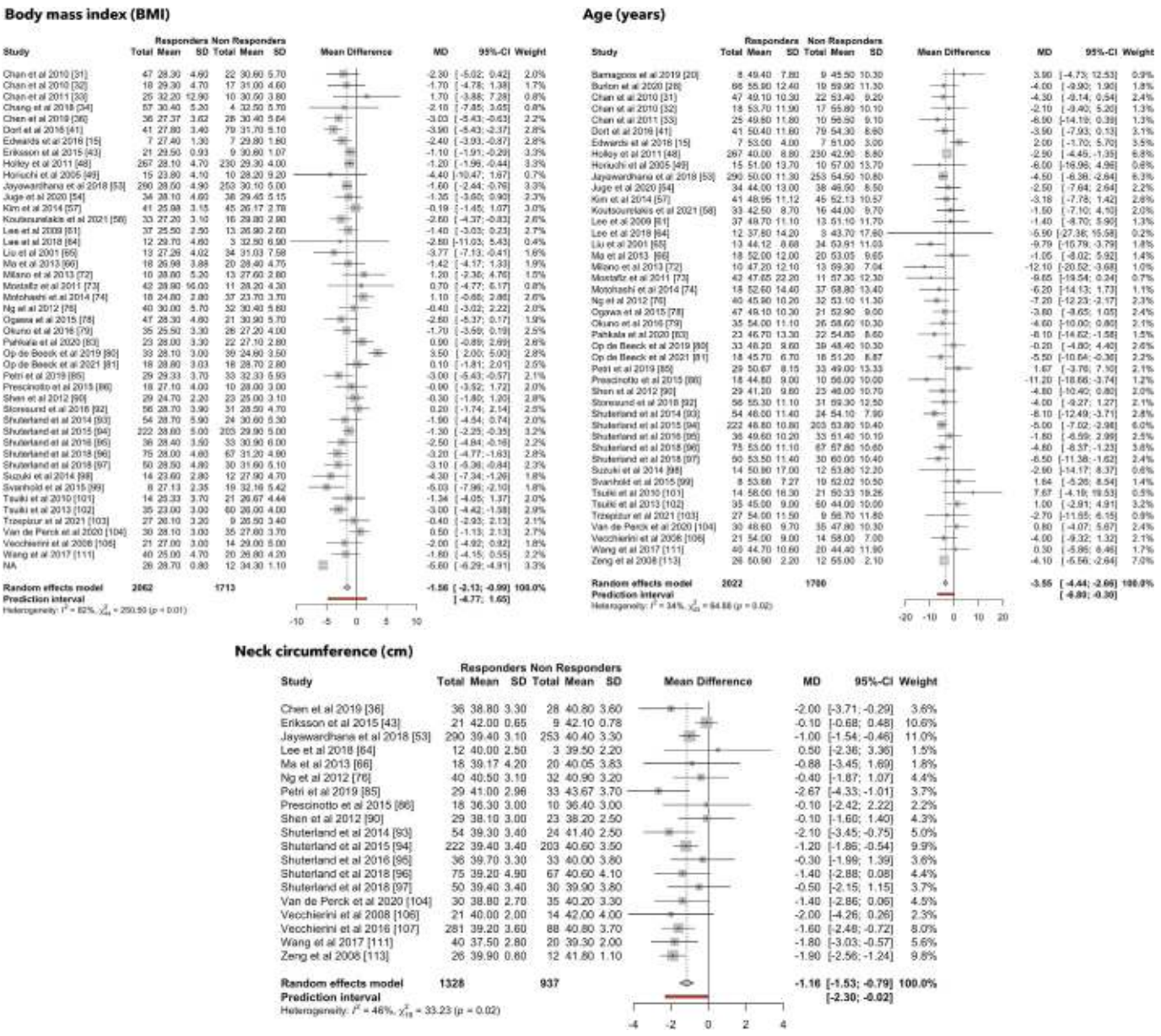

Fig. 3. Forest plot of the significant clinical variables: body mass index, age (y), neck circumference (cm).

responders is 8.36 ± 2.28 cmH_2O (95% CI: −1.94; −0.55; p = 0.0004; GRADE tool: moderate evidence profile) (see Fig. 5).

The forest plots of the rest of the non-significant variables are indexed in the supplementary material (Figs. S4–S23).

Table 2 describes the results of the meta-analysis by subgroups of significant variables. Regarding the device type, significant results were found only in "age" variable. The biblock adjustable device is the one that provides the "weight" of the significance.

As for the meta-analysis according to the criteria of responders used, interesting results have been found with respect to criterion three (AHI <10 + reduction >50% AHI). Criterion three is the one that provides the "weight" of significance for the variables "BMI", "age", "neck circumference", "anterior facial height", "posterior facial height", "third cervical − hyoid", and "optimal CPAP pressure".

For the rest of the variables, there was no statistically significant difference between both subgroups (MAD type and responders criteria).

Discussion

The last European Respiratory Society guideline considered CPAP and MAD as equal in patients with mild to moderate OSA, or severe OSA in adult patients who do not tolerate CPAP therapy or refuse surgery [114]. However, a major limitation is the variability in the efficacy of oral devices, as it is an effective treatment for 60–70% of the patients [1]. Despite CPAP is more effective in reducing the AHI than MAD, there is increasing evidence that MAD is better tolerated with a compliance of 1.1/per night higher than CPAP [11]. Therefore, given that the ability to identify which patients will receive therapeutic benefit is currently a challenge, the aim of this study has been focusing on identifying the phenotypic characteristics of responders to oral devices, focused on adult patients.

This review significantly updates this topic because it includes a large number of articles and variables studied in the meta-analyses, thus offering new information for decision-making.

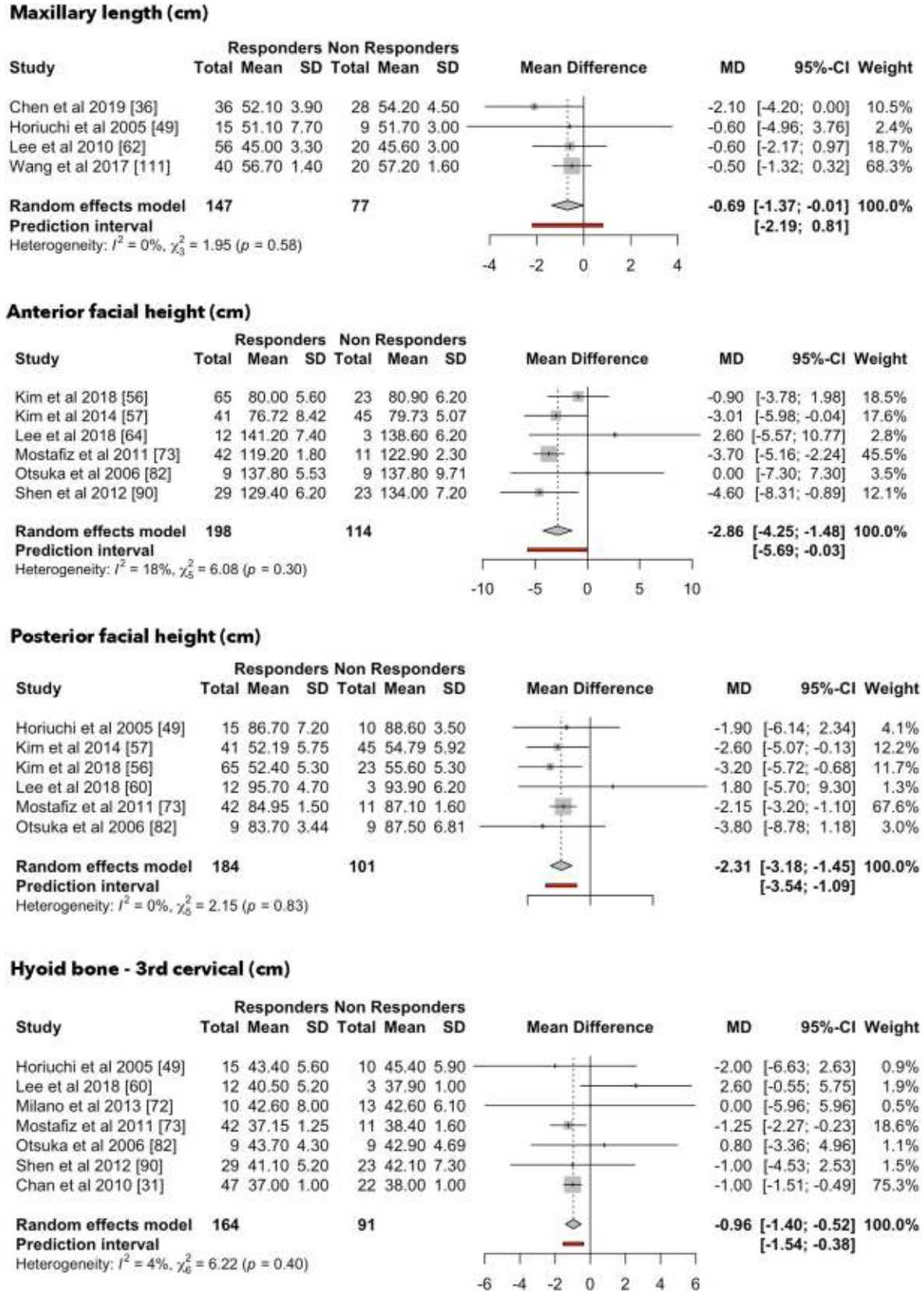

Fig. 4. Forest plot of significant cephalometric variables: maxillary length (cm), anterior facial height (cm), posterior facial height (cm), distance third cervical – hyoid bone (cm).

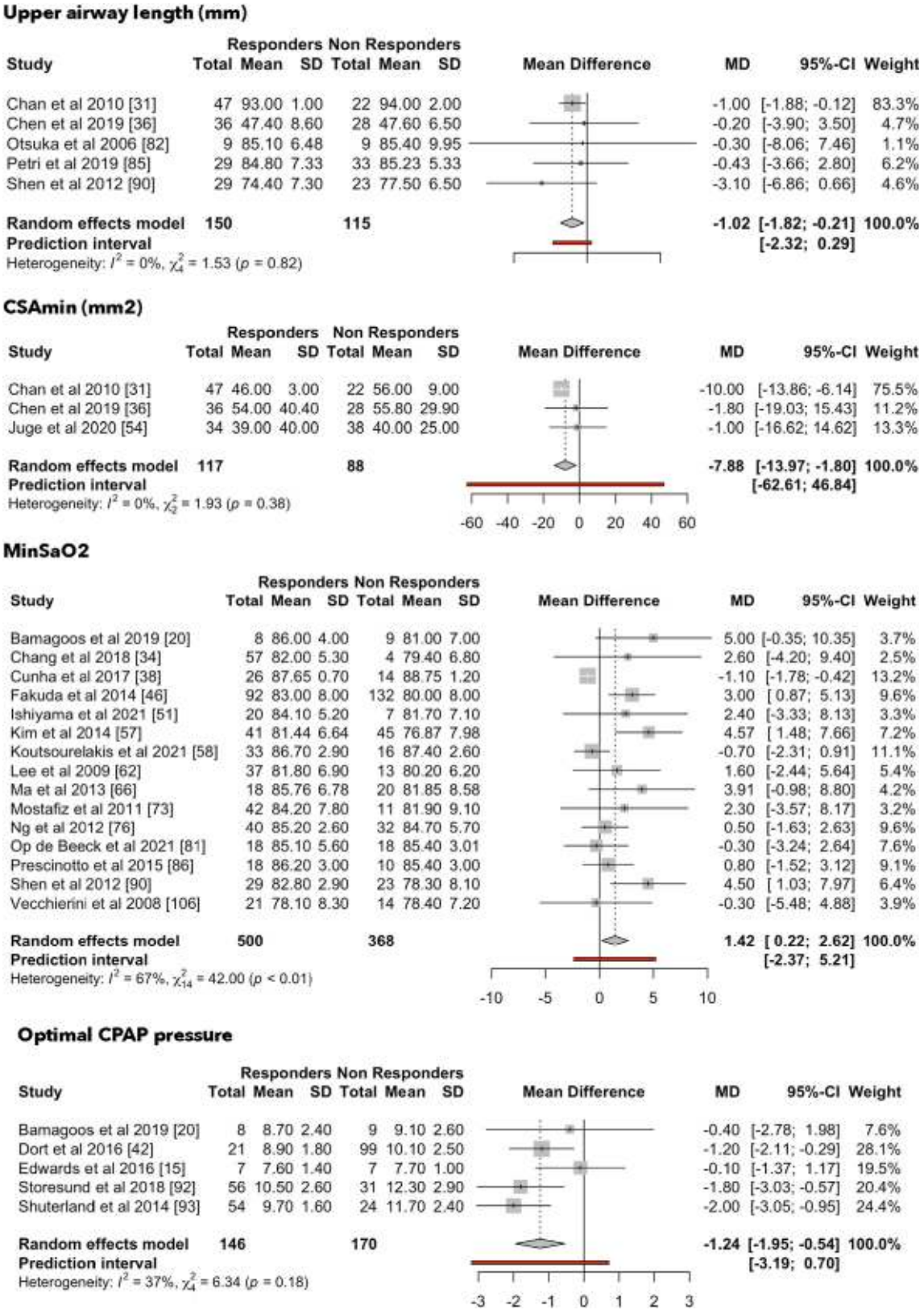

Fig. 5. Forest plot of the significant physiological, polysomnographic and treatment variables: upper airway length (mm), CSAmin (mm^2), $MinSaO_2$ (%) and optimum CPAP pressure (cmH_2O). Abbreviations: CPAP continuous positive airway pressure; CSAmin = minimum airway cross-sectional area; $MinSaO_2$ = minimum oxygen saturation.

Table 2
Meta-analysis by subgroups of significant variables.

Variables	Criteria		N Studies (K)	Mean difference (IC 95%)	I^2 (%)	P-value
Body mass index	MAD type	1	36	**−1.63 (−2.42; −0.85)**	84.6	0.9706
		2	6	**−1.70 (−2.87; −0.52)**	49.5	
		1 and 2	2	−1.17 (−5.28; 2.95)	50.1	
	Responders criterion	1	3	−0.49 (−2.19; 1.20)	57.1	0.1557
		2	16	−1.30 (−2.95; 0.35)	91.8	
		3	24	**−1.85 (−2.39; −1.30)***	42.1	
		1 and 2	1	**−4.30 (−7.34; −1.26)**	–	
Age	MAD type	1	35	**−3.90 (−4.75; −3.05)***	23.3	0.010
		1 and 2	2	−4.38 (−9.13; 0.38)	0.0	
		2	5	0.01 (−2.49; 2.50)	4.8	
	Responders criterion	1	2	−4.50 (−9.20; 0.20)	56.8	0.9799
		2	16	**−3.45 (−5.03; −1.88)**	41.8	
		3	23	**−3.60 (−4.78; −2.42)**	25.1	
		1 and 2	1	−2.90 (−14.17; 8.37)	–	
Neck circumference (cm)	MAD type	1	17	**−1.27 (−1.55; −0.99)**	4.0	0.9941
		2	2	−1.26 (−3.77; 1.24)	87.8	
	Responders criterion	2	7	**−1.57 (−1.99; −1.15)**	0.0	0.0681
		3	12	**−0.98 (−1.46; −0.50)**	46.7	
Maxillary length (mm)	MAD type	1	2	−0.99 (−2.45; 0.45)	48.3	0.9319
		1 and 2	1	−4.06 (−4.96; 3.76)	–	
		2	1	−0.60 (−2.17; 0.97)	–	
	Responders criterion	2	2	−0.52 (−1.25; 0.21)	0.0	0.2099
		3	2	−1.81 (−3.71; 0.07)	0.0	
Anterior facial height (mm)	MAD type	1	5	−2.61 (−4.51; 0.71)	34.2	0.8242
		2	1	−3.01 (−5.98; 0.04)	–	
	Responders criterion	1	1	0.00 (−7.30; 7.30)	0.0	0.0812
		2	2	−0.51 (−3.23; 2.19)	0.0	
		3	3	**−3.68 (−4.92; −2.44)***	0.0	
Posterior facial height (mm)	MAD type	1	4	**−2.29 (−3.24; −1.35)**	0.0	0.9560
		1 and 2	1	−1.90 (−6.14; 2.34)	–	
		2	1	**−2.60 (−5.07; −0.13)**	–	
	Responders criterion	1	1	−3.80 (−8.78; 1.18)	–	0.8209
		3	3	**−2.20 (−3.14; −1.26)***	0.0	
		2	2	−2.00 (−6.19; 2.19)	34.8	
3rd cervical − hyoid (mm)	MAD type	1	5	−0.80 (−1.61; 0.01)	32.5	0.6162
		1 and 2	1	−2.00 (−6.62; 2.62)	–	
	Responders criterion	1	1	0.80 (−3.36; 4.96)	0.0	0.4330
		2	2	0.45 (−3.01; 3.91)	79.5	
		3	3	**−1.26 (−2.22; −0.31)***	0.0	
Upper airway length (mm)	MAD type	1	4	**−1.05 (−1.89; −0.22)**	0.0	0.7135
		2	1	−0.43 (−3.66; 2.80)	–	
	Responders criterion	1	1	−0.30 (−8.05; 7.46)	–	0.9752
		2	1	**−1.00 (−1.88; −0.12)**	–	
		3	3	−1.15 (−3.19; 0.89)	0.0	
CSAmin (mm^2)	MAD type	1	3	−9.13 (−12.79; −5.48)	0.0	–
	Responders criterion	**2**	1	**−10.00 (−13.86; −6.14)**	–	0.1651
		3	2	−1.36 (−12.93; 10.21)	0.0	
$MinSaO_2$ (%)	MAD type	1	10	0.41 (−0.73; 1.56)	49.5	0.0054
		2	4	3.14 (1.60; 4.69)	0.0	
	Responders criterion	1	1	2.60 (−4.20; 9.40)	–	0.5276
		2	5	0.51 (−0.96; 1.97)	0.0	
		3	8	1.72 (−0.06; 3.52)	80.5	
Optimal CPAP pressure	MAD type	1	4	**−1.09 (−1.94; −0.24)**	45.6	0.3481
		1 and 2	1	**−1.80 (−3.03; −0.57)**	–	
	Responders criterion	1	1	−0.40 (−2.78; 1.98)	0.0	0.1537
		2	2	−0.74 (−1.81; 0.32)	47.1	
		3	2	**−1.92 (−2.71; −1.12)***	0.0	

Abbreviations. * Significant IC 95%. AHI: apnea−hypopnea index; CSAmin: minimum airway cross-sectional area; CPAP: continuous positive airway pressure; I^2: heterogeneity; MAD: mandibular advancement device; $MinSaO_2$: minimum oxygen saturation. **Criteria**. MAD type 1: adjustable biblock; MAD type 2: monoblock. Responders criterion 1: AHI <10; Responders criterion 2: AHI reduction >50%; Responders criterion 3: AHI <10 + reduction >50%.

In order to reduce the heterogeneity of the results in relation to the type of devices used (monoblock or biblock), statistical analysis by subgroups was performed. In general, the type of device has not affected the results of the meta-analysis (Table 2).

On the other hand, regarding the variability in the definition of responders, the main criteria have been grouped to homogenize the results of the meta-analysis. The literature that has focused on analyzing the different success criteria in OSA, has determined the criteria used in this meta-analysis (criterion 1, 2 and 3) as the most decisive for the diagnosis [115]. In the results, criterion three (AHI <10 and AHI reduction >50%) has obtained the "weight" of significance in certain variables (Table 2). Therefore, this criterion should be taken into consideration for future studies to predict OSA treatment by MAD.

In terms of clinical characteristics, the results of the present meta-analysis indicated that responders to oral device therapy tended to be younger in age, specifically 3.6 y younger (mean non-responders 51.67 ± 10.2 y), with lower BMI and neck circumference.

These results coincide with the previous review by Chen H et al. [14]. However, the data now acquire greater validity because the

number of patients included in the meta-analysis has increased considerably (age n = 1854 to n = 3722; BMI n = 1791 to n = 3775; NC n = 1215 to n = 2265). The results of the prediction interval in the meta-analysis for the variables "age" and "NC" offers a great validity to these phenotypes.

It has been experimentally demonstrated that, with aging, the hypoxic response during sleep decreases, the breathing muscles are less capable of generating tension [65] and resisting fatigue, and there is more instability in the ventilatory system during sleep [116]. In addition, upper airway size has been shown to decrease with age in both men and women [117]. Therefore, it appears that both the structure and function of the superior airway deteriorate with aging, so it might be expected that the efficacy of OA would be compromised with increasing age.

On the other hand, high BMI are associated with fat deposition in pharyngeal wall and base of the tongue, which can narrow the diameter of the pharynx and increase the collapsibility of the upper airway [118].

However, many responders fall outside the currently recommended limits for clinical characteristics, and so characteristics alone are not powerful enough predictors and ultimately alternative objective predictive methods are needed to predetermine treatment outcome [94].

Although ESS was not a significant predictor in the results of the meta-analysis, this parameter should be considered equally because sleepiness has been associated with the incidence of cardiovascular diseases and heart failure compared to those that have not ESS [119].

Traditionally, since the study by Eveloff et al., a shorter distance from the hyoid bone to the mandibular plane has been related to a greater response [44,72,87,91]. However, it should be noted that the first articles demonstrating this association had a small sample size. Subsequently, in published articles with a larger sample size, this association has not been proved [51,56,82], and even an inverse association was found [65,88,91]. This association was not found in the meta-analysis. However, a shorter distance from the hyoid bone to the third cervical vertebra was related to a successful treatment with OA. In the review by Chen H et al., no significant differences were found [14]. By increasing the number of patients included, a significant difference between the two groups is demonstrated with a very low heterogeneity (I^2 4%) and a very reliable prediction interval (−1.73; −0.16). Therefore, the measurement of this variable should be considered for future studies.

Regarding the relationship to the anatomical balance, it is likely that a reduced size of the bony compartment and an increased expansion of the surrounding soft tissues results in an increased collapsibility due to the soft tissue pressure on the airway [73]. Based on the meta-analysis, responders have a lower anterior and posterior facial height (with a very reliable prediction interval), and a shorter maxillary length, and thus these results suggest that, with these characteristics, the intermaxillary space available for the tongue is reduced, and after insertion of a mandibular advancement device, this relationship is normalized. Consequently, this relationship reinforces the finding that a good anatomical balance is a predictive factor of success in the treatment with OA [38]. The results of the meta-analysis confirm the importance of determining anatomical balance in future prospective studies.

In relation to the soft tissue characteristics, several studies in the systematic review revealed that responders have a larger tongue in relation to the size of the available oral cavity, which contributes to increased collapsibility of the airways [73,90]. However, in the meta-analysis results, no significant relationship was found in the soft palate and tongue characteristics. It should be noted that this relation was only quantitatively analyzed in four studies, so this relation must be interpreted carefully. More randomized controlled trials are needed to determine this relationship.

Regarding physiological anatomical characteristics, in the meta-analysis results, the airway length in responders is shorter than that of non-responders ($p < 0.05$). This is because longer airways are more collapsible, and this characteristic is mostly associated with men [117].

Considering that OA prevent airway closure by displacing the mandible and attached soft tissues forward, it is believed that the location of collapse in the upper airway during sleep is an important factor to consider in predicting success or failure [30]. Nevertheless, quantitative results regarding location and physiological characteristics could not be unified for meta-analysis.

Regarding the qualitative analysis, most studies suggest that a primary oropharyngeal collapse is an important predictor of OA response [25,75,90,105,110]. However, the results vary among the different studies [23,35,74]. These differences could be due to the diagnostic tool used. Guijarro-Martínez and Swennen et al. described CBCT obstacles which include the breathing phase, tongue position, mandibular morphology, and three-dimensional anatomical definitions [120].

Secondly, differences in the patients' position during the image study may also influence the results due to a gravity issue, as the anatomy of the upper airway is different in the supine and upright positions [36]. In several studies patients were standing [82] or sitting [45], while in others they were in the supine position [36]. The supine position, although it cannot exactly reproduce the actual upper airway morphology during sleep, is closer to reality than the upright position. In future studies, the use of DISE with simulation bite as a prognostic indicator for treatment with MAD should be considered as it offers a reproducible technique for determining the sites of obstruction in OSA subjects [30].

In relation to polysomnographic characteristics, even though numerous studies have observed that patients with lower apnea and hypopnea indexes respond better to sleep apnea treatment [14,16–18,34,39,47,48,53,54,57,70,73,79,86,90,92–94,96,101,111,112], in the meta-analysis results this characteristic did not reach significance, although there was a trend in AHI significance (mean of AHI in responders is 26.14 ± 11.38 events/h and in non-responders is 32.06 ± 14.64 events/h). This could be influenced by the night-to-night variability of this parameter and the AHI underestimation effect of respiratory polygraphy used for diagnosis in some of the articles reviewed. Therefore, AHI alone is not a reliable characteristic in predicting oral device treatment.

The most recent literature shows that this parameter has severe deficiencies in terms of reproducibility and validity as predictor, yet it is the most widely used parameter to establish a diagnosis of OSA [121]. Therefore, we must analyze this parameter together with other parameters such as hypoxemia. It was observed that responders present a higher $minSaO_2$, so we must consider this parameter. Furthermore, Azarbarzin A et al. demonstrated that the more severe is the hypoxia (expressed as hypoxic burden), the worse is the cardiovascular disease outcome, and noted that the AHI alone did not predict outcomes on its own [122].

On the other hand, PSG sleeping posture is an important tool in predicting the success or failure of MAD treatment [33,37,48,63,65,85,104,112]. However, the different definitions used to describe positional OSA make it difficult to make the comparison between different studies, and thus the quantitative analysis of the results has not been possible.

Patients with supine-dependent OSA reflect normal pharyngeal morphology with a normal airway in the lateral dimension, whereas patients with apneas in the lateral position have a narrow airway in the lateral dimension. Therefore, problems maintaining airway patency in the lateral sleeping position indicate a high risk

of apneas, since the airway is usually more stable in the supine than in the lateral position. Sleeping in the lateral position is probably a protective mechanism against sleep apnea, as the pharynx is more collapsible in the supine position than in the lateral position, and supine-dependent apneas are more severe and lead to greater arousals [118].

Knowing the CPAP pressure level in those patients who have not tolerated this treatment, could be a valuable diagnostic tool for predicting the treatment response of mandibular advancement devices. In the meta-analysis results, it has been obtained that responders to OA treatment required a lower optimal CPAP pressure level. It should be considered that those patients with a deeper severity of the illness will require higher CPAP pressure to re-establish the airway patency, so those patients who have required lower pressure to adjust the CPAP are associated with a lower severity and collapsibility, therefore respond better to OA treatment [21,123]. The mean CPAP pressure of non-responders >8 cmH_2O (8.36 ± 2.28) is 1.2 cmH_2O higher than responders; this finding points out this parameter as an indirect marker of OSA severity phenotypes where an optimal CPAP pressure less than 8 cmH_2O is associated with a critical occlusion pressure of UA (Pcrit) less than −2.5 cmH_2O, related to a low UA collapsibility [124,125].

OSA is a heterogeneous disorder with many contributing factors. While all patients have an unfavorable airway anatomy (e.g., a narrow, collapsible airway), a number of non-anatomical features called PALM (Pcrit, arousal threshold, loop gain and muscle responsiveness) also contribute, which aggravate the disease, such as increased collapsibility or Pcrit, a lower arousal threshold, ventilatory control instability (increased loop gain), and dysfunction of the upper airway dilator muscles [123].

Several studies have shown that responders have a greater stability of ventilatory control, reflected by lower baseline loop gain using routine PSG as a diagnostic tool [15,18,21,81]. It has also been demonstrated that responders have a lower pharyngeal collapsibility under passive conditions or passive Pcrit conditions, i.e., when the dilator muscles are relatively inactive [18,19,21,71,93,94,109] and the micro-awakening threshold is lower [81]. In addition, a lower pharyngeal muscle compensation was associated with a higher device efficacy [66]. Ma SY et al. demonstrated that responders showed increased muscle activity in the masseter, submandibular and anterior temporalis muscles at rest, with a 75% advancement [66]. With mandibular advancement, neuromuscular stimulation occurs, resulting in an enlargement of the velopharynx and oropharynx, increasing the airflow [126].

The results of this meta-analysis suggest that the set of significant variables could be grouped into a predictive model for the success of obstructive sleep apnea treatment using mandibular advancement devices. Future randomized controlled trials should provide data on which of these variables are the most predictive.

Limitations

The present systematic review and meta-analysis unifies all available information regarding possible predictors of treatment success and failure with oral devices. Although there are key findings that help the clinician to individualize treatment, standardization is required both in the main definition of “successful treatment” and of “positional OSA”, which makes it difficult to generate comparisons between the existing literature. The definition of responders in other previous studies are just as heterogeneous and it would be interesting to consider homogenizing this criterion for future studies.

The non-tolerating CPAP patients have not been controlled in the present meta-analysis because the studies included did not make differentiation of the MAD as a first treatment option. It would be interesting to carry out an ad-hoc study to observe this parameter in more detail.

The GRADE tool for grading recommendations in clinical practice has been used (see Table S7 in supplementary material). This scale determines an initial ‘low evidence’ for observational studies and an initial ‘high evidence’ for RCTs. Assuming that most of the studies that have been included in the present study are observational studies, the overall evidence for the results is ‘low’ to ‘moderate’. However, the heterogeneity of the results is generally low and the prediction intervals of the results reinforce the results obtained. There is moderate/limited confidence in the effect estimate and there is a probability that the real effect is far from the estimated effect. Long-term RCTs with a large sample size are needed to confirm the results obtained.

In the present study it was not possible to unify values of the non-anatomical characteristics for the meta-analysis due to the heterogeneity of the presentation of the results. The need for long-term randomized clinical trials with a significant sample is suggested which, in addition to analyzing clinical, polysomnographic and anatomical variables, also study the novel non-anatomical variables that may contribute significantly to understanding the pathogenesis of OSA.

Other information

Protocol and registration

The present systematic review and meta-analysis was previously registered in PROSPERO under registration number CRD42020180447.

Conflicts of interest

All authors declare no potential conflict of interest related to the study.

Practice points

Responders to apnea treatment using mandibular advancement devices (**GRADE tool: low to moderate evidence profile)** are characterized by:

1. Clinical traits: younger patients, smaller neck circumference, lower body mass index.
2. Anatomical traits: a shorter maxillary length, lower anterior and posterior facial height, a shorter distance from the hyoid bone to the third cervical vertebra, a shorter airway length, a smaller minimum airway cross-sectional area.
3. PSG characteristics: higher minimum oxygen saturation during sleep.
4. Treatment characteristics: lower optimal CPAP pressure.
5. The design of device (monoblock or adjustable biblock) used does not seem to affect the prediction of response to obstructive sleep apnea treatment.
6. Criterion 3 of responders (AHI <10 and reduction AHI >50%) should be considered to predict the response to sleep apnea treatment by oral devices.

Research agenda

In future, we need to:

1. Standardize the main definition of "successful treatment" and of "positional OSA". According to the meta-analysis results by subgroup of the present review, criterion 3 of responders must be considered to standardize this definition.
2. Use the drug-induced sleep endoscopy with simulation bite as a prognostic indicator for treatment with mandibular advancement devices, as it is an acceptably reproducible technique for determining the sites of obstruction in obstructive sleep apnea subjects.
3. Develop personalized medicine in oral appliances management and to give specific recommendations for the optimal device design in specific phenotypes of obstructive sleep apnea patient.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2022.101644.

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