Mandibular Jaw Movement Automated Analysis for Oral Appliance Monitoring in Obstructive Sleep Apnea: A Prospective Cohort Study

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Author contributions

JLP, JBM and NNLD designed the study.

JLP, JBM and EC conducted the research procedure and had full access to all study data.

JLP, JBM, NNLD, RT, and SB performed data analysis.

JLP, JBM, PC, GL, AB, and AM have personally reviewed the data, verified the statistical methods employed for all analyses, and confirms an understanding of these analyses, that the methods are clearly described and that they are a fair way to report the results.

JLP, JBM and NNLD prepared the first draft of the manuscript.

GL, CP, AB reviewed and edited the final manuscript.

All authors made the decision to submit the manuscript for publication and assume responsibility for the accuracy and completeness of the analyses and for the fidelity of this report to the study protocol.

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NNLD is an employee of Sunrise.

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AM reports income from Jazz, Zoll, Sunrise, Livanova, Eli Lilly related to medical education.

JBM is a scientific advisor to Sunrise and has been an investigator in pharmaceutical trials for Jazz Pharmaceuticals and Theranexus.

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ABSTRACT

Rationale: Oral appliances are second-line treatments after continuous positive airway pressure (CPAP) for obstructive sleep apnea (OSA) management. However, the need for oral appliance titration limits their use due to monitoring challenges to assess the treatment effect.

Objectives: To assess the validity of mandibular jaw movement (MJM) automated analysis compared to polysomnography/polygraphy (PSG/PG) in evaluating the effect of oral appliance treatment and the effectiveness of MJM monitoring for oral appliance titration at home in OSA patients.

Methods: This observational, prospective study included 135 OSA patients eligible for oral appliance therapy. The primary outcome was the apnea-hypopnea index (AHI), measured through in-laboratory PSG/PG and MJM-based technology. Additionally, MJM monitoring at-home was conducted at regular intervals during the titration process. The agreement between PSG/PG and MJM automated analysis was evaluated using Bland-Altman analysis. Changes in AHI during the home-based oral appliance titration process was evaluated using GLMM and GEE models.

Measurements and Main Results: The automated MJM analysis demonstrated strong agreement with PG in assessing AHI at titration end, with a median bias of 0.24/h (limits of agreement: –11.2 to 12.8/h). The improvement of AHI from baseline in response to oral appliance treatment was consistent across 3 evaluation conditions: in-laboratory PG (–59.6%; –59.8% to –59.5%), in-laboratory automated MJM analysis (–59.2%; –65.2% to –52.2%) and at-home automated MJM analysis (–59.7%; –67.4% to –50.2%).

Conclusions: Incorporating MJM automated analysis into the oral appliance titration process has the potential to optimize oral appliance therapy outcomes for OSA.

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Obstructive sleep apnea (OSA) is a highly prevalent disorder that has deleterious health consequences for individuals (including cardiovascular and metabolic comorbidities) and imposes a high burden on the health system (1,2).

Continuous positive airway pressure (CPAP) therapy is the first-line treatment for moderate-to-severe OSA. However, long-term adherence to CPAP remains a challenge, with nearly 50% of individuals with OSA having stopped using CPAP at 3 years after therapy initiation (3). Oral appliances have traditionally been recommended for second-line therapy in individuals intolerant of, or refusing, CPAP (4). However, in many countries, the indication for these devices has been expanded to include primary therapy for symptomatic individuals with different levels of OSA severity who have a low comorbidity burden (5,6).

Titratable two-piece custom-made mandibular advancement devices (MADs) prescribed and managed by dentists are widely accepted as the gold standard oral appliance therapy. Although CPAP is more effective than MADs for reducing the apnea-hypopnea index (AHI) and oxygen desaturation index (ODI), MADs have shown comparable effects to CPAP on sleep structure and health outcomes (7,8). Additionally, patient preference and adherence favor oral appliance therapy, thereby balancing slightly lower efficacy (9). Nevertheless, practical limitations to the implementation and titration of MADs continue to limit the large-scale adoption of such therapy in clinical practice. Furthermore, complexities in the multidisciplinary care pathway can result in delays in treatment initiation and is associated with a high rate of loss to follow-up in the absence of sleep studies to assess MAD efficacy (10). Therefore, there is a need to design new care pathways that incorporate digital medicine solutions for MAD titration to achieve optimal efficacy of treatment.

Previous research has demonstrated the reliability of mandibular jaw movement (MJM) monitoring coupled with machine learning analysis as a diagnostic tool for OSA (11-15). This

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approach also allows home-based evaluations over multiple nights. However, further validation is required to establish the effectiveness and reliability of MJM analysis in individuals using custom-made MADs that position the mandible in a forward and downward direction as this could impact the accuracy of MJM monitoring.

This study aimed to validate automated MJM analysis compared to in-laboratory polysomnography (PSG)/polygraphy (PG) in assessing the effectiveness of MAD treatment, and to evaluate suitability of automated MJM analysis for at-home monitoring of MAD treatment in individuals suffering from OSA.

METHODS

Study Design and Participants

This prospective cohort study included consecutive adults referred for assessment of suspected OSA at the sleep laboratory of CHU-UCL Hospital (Namur, Belgium). The protocol was approved by the Comité d'Ethique Hospitalo-Facultaire-Universitaire in Liège, Belgium (IRB #00004890). All participants provided written informed consent.

Baseline Assessments and OSA Diagnosis

Baseline assessments included in-laboratory diagnostic PSG (Somnoscreen Plus, Somnomedics, Randersacker, Germany) with simultaneous MJM recording using the Sunrise technology (Sunrise, Namur, Belgium) (see online data supplement for further details on this technology) (11-15) (Figure 1). PSG recordings were manually assessed using the American Academy of Sleep Medicine (AASM) criteria (16,17) by two experienced scorers who were unaware of treatment conditions (inter-observer agreement of 92.1% [95% confidence interval (CI) 89.1 to 94.2]) and of results of automated MJM analysis. Hypopnea events were

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defined as a ≥30% drop in flow signal amplitude for at least 10 seconds, associated with either a ≥3% oxygen desaturation or an arousal. Apnea events were defined as a drop of ≥90% of pre-event baseline for at least 10 seconds (16,17).

The OSA diagnosis was confirmed based on the International Classification of Sleep Disorders-3 (ICSD-3) criteria (18). OSA was defined as an AHI of ≥5/h, with severity categorized as mild (AHI 5 to <15/h), moderate (AHI 15 to <30/h) or severe (AHI ≥30/h).

Oral Appliance Therapy and Titration

Participants eligible for oral appliance treatment were individuals with a confirmed OSA diagnosis, based on in-laboratory PSG. MAD therapy was offered to participants with OSA who did not have overt cardiovascular or metabolic comorbidities. However, MAD was not suitable to patients exhibiting severe sleepiness or for professional drivers, and those with compromised stomatognathic situation (<8 teeth per arch, temporomandibular disorder, periodontitis).

The MAD used was a two-piece custom-made (NOA; OrthoApnea, Malaga, Spain) (19) (see online supplement for further details).

The titration protocol for oral appliance therapy was a dynamic process involving periodic evaluations and adjustments, with a total duration varying from 2 to 6 months. Continuous engagement was maintained with participants through weekly telephonic consultations, focusing on evaluating the persistence or worsening of symptoms like snoring (as reported by the bedpartner), fatigue or excessive daytime sleepiness. The titration began with a MAD set at 60% of the maximal voluntary advancement. Subsequently, the MAD was adjusted under the direction of the sleep physician, advancing in increments of 1 mm every few weeks, as tolerated, until reaching the maximum comfortable limit.

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Treatment Assessment and Follow-up

There is a specific care pathway for ongoing reimbursement of MAD therapy in Belgium that requires objective demonstration of treatment benefit on PG within 6 months of starting MAD therapy. Therefore, all participants underwent in-laboratory PG at the completion of MAD titration, along with simultaneous MJM recording (Figure 1). In addition, single-night home sleep studies using the MJM monitoring system were performed at regular intervals (Figure 1).

These tests were conducted at various stages: (1) prior to starting MAD therapy; (2) at the start of MAD titration (set at 60% of maximum active protrusion); (3) at an intermediate titration level (with mandibular advancement of either +1 mm or + 2 mm); and (4) at the final level of mandibular advancement (with an additional 1 mm protrusion compared to the intermediate level, i.e., either +2 mm or +3 mm) (Figure 1). The tests were done under stabilized clinical condition, ensuring that the advancement level was maintained consistently for at least 10-15 days without any associated discomfort. Importantly, the results of these home sleep tests were not used as criteria for adjusting mandibular advancement levels and were kept undisclosed to the treating physician during the study. For each of the four above-mentioned assessments, participants were required to complete digital surveys designed to collect information regarding device usage, treatment effectiveness, OSA symptoms, as well as adverse events (both in terms of frequency and intensity). Responses were measured on a scale of 0 to 10, where 0 indicated the absence of symptoms or side effects, and 10 indicated severe symptoms or side effects. For the primary analyses, all included patients adhered to the criteria of MAD therapy compliance, defined as using the device for at least 5 hours per night on more than 90% of nights.

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Outcomes

The primary endpoint was the change in AHI from baseline to the end of titration protocol, determined using PG or MJM automated analysis. Secondary endpoints included the change in ODI and subjective measurements of OSA-related symptoms (sleepiness, vigilance, fatigue), satisfaction with sleep quality, and the tolerability of MAD therapy.

Statistical Analysis

Based on the results of simulations (Figure E1, Figure E2), it was determined that a sample of 90 to 100 participants would be sufficient to validate an absolute mean limit of agreement (LOA) measurement bias for AHI of 5/h to 14/h against the clinical acceptability threshold of 25/h, and to detect a relative change in AHI of 40–70%, with a statistical power of 0.8 and type I error of 0.05 (see online data supplement, Figure E1 & E2 for full details).

Agreement between AHI measurements determined by in-laboratory PSG or PG, and simultaneous MJM monitoring was evaluated using Bland-Altman analysis and LOA values (and the corresponding 5^{th} and 95^{th} percentiles) were calculated. A bias-corrected accelerated bootstrap process was used to determine the 95% CI of the results.

Average treatment effect of MAD therapy was determined by calculating the absolute and relative changes in the evaluated parameters between baseline and final degree of MAD advancement. Estimation of the change in AHI between baseline and final conditions was based on a generalized linear mixed-model (GLMM) via GAMLSS package (20) with an appropriate distribution law for the response variable (a Gamma distribution for AHI and ODI, a negative binomial distribution for occurring rate of apnea-hypopnea events, and an inflated Beta distribution for normalized questionnaire scores) and included subject-specific

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random effects. The potential effect of total sleep time (TST) variation was adjusted using the same model framework with number of apnea-hypopnea events as outcome and TST included as a covariate. Change in AHI at home measured with MJM automated analysis in response to MAD titration was evaluated using a generalized estimating equation (GEE) model (21) with Gamma distribution. Confidence intervals for the marginal effects were determined by the delta method using the marginal effects package (22).

Data analysis was carried out using R programming language (https://www.R-project.org/). Statistical inferences were based on null hypothesis testing at a significance level of 0.005.

RESULTS

Study Population

The study population included 135 individuals, 30 of whom were lost to follow-up (due to the impact of the COVID-19 pandemic [n=18] or inadequate protocol compliance [n=12]). Full data from home monitoring questionnaires were available for 93 participants. The study population was predominantly male, middle-aged, and overweight; snoring and daytime symptoms of OSA were common (Table 1). Baseline in-laboratory PSG showed altered sleep efficiency, sleep fragmentation and moderate-to-severe OSA, with events occurring most frequently in the supine position. The mean duration of follow-up was 5.23 ± 0.40 months. Initial, intermediate, and final protrusion levels were 60.0 ± 0.00, 68.15 ± 1.66 and 76.56 ± 3.67% of maximum active protrusion, respectively (Table E1).

AHI Estimation: Automated MJM analysis vs. PSG/PG

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Visualization of the MJM bio-signals with manually scored data from conventional PSG or PG showed a strong agreement between both methods (i.e., MJM vs. either PSG or PG) (Figure E3). The AHI measurement bias was randomly and normally distributed at both baseline and final assessments, and the MJM automated analysis consistently replicated the same AHI distribution shape as captured by PSG and PG across the entire measurement range (Figure 2). At baseline, the MJM automated analysis slightly underestimated the AHI compared to in-laboratory PSG, with a median bias of –4.8/h (95% CI –5.9; –3.1). The LOA was –22.7 to 11.7/h. At the end of MAD titration, median bias of MJM analysis was 0.2/h (95% CI –1.4; 2.1), which is clinically acceptable, and the LOA values had a narrower range (from –11.2 to 12.8/h).

PSG/PG data showed a significant reduction in AHI from baseline to the end of MAD titration (absolute change –15.6/h [95% CI –15.6; –15.5]; relative change –55.6% [95% CI –55.8; –55.5]) (Figure 3, Table 2). In the subgroup of participants who underwent both in-laboratory PG and home-based MJM monitoring after MAD titration (n=93), the average reduction in AHI measured with MJM analysis (–59.7% [95% CI –67.4; –50.2]) was very similar to that observed with in-laboratory PG (–59.6% [95% CI –59.8; –59.5) (Table 2, Figure 3). By conducting a supplementary analysis that specifically examined the frequency of apnea-hypopnea events, incorporating TST as a covariate (refer to Table E2), we have substantiated that the changes in the observed AHI were not impacted by fluctuations in TST.

MJM-Based Analysis for the Evaluation of MAD Titration Efficacy and AHI Response at Home

At-home MJM-based monitoring showed a progressive and significant improvement in the AHI as the degree of protrusion increased during MAD titration (Figure 4, Table E3). Even at

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the initial titration level (SP for starting point) set at 60% of the maximum active protrusion, there was a significant reduction in the AHI (–10.3/h, –47.7%; p<0.0001) from baseline. Further reductions in AHI were seen as MAD protrusion increased with a reduction of –12.7/h (–58.6%) from baseline to intermediate protrusion (T1), and of –13.0/h (–59.7%) from baseline to final protrusion (T2) (Table E3).

Significantly, at the initial protrusion level (SP), 47 out of 93 participants (50.5%) demonstrated an AHI improvement of more than 50% from baseline. The responder rates at intermediate and final levels were 64.5% (60 out of 93) and 65.6% (61 out of 93), respectively. Furthermore, the responder rates associated with a normalized AHI (≤ 5 events/h) were 22.6% (21 out of 93), 32.3% (30 out of 93), and 46.2% (43 out of 93) at the initial, intermediate, and final levels of advancement, respectively.

There was also a significant ODI improvement between baseline and the final protrusion level with an absolute change of –7.9/h (95% CI –7.9; –7.9) and a relative change of –41.0% (95% CI –41.2; 40.9).

Effects of MAD on OSA Signs and Symptoms

The use of a MAD was associated with significant improvements in sleep quality, snoring, morning fatigue, headache, dry mouth, and daytime sleepiness (Table 3, Table E4).

Tolerability

Patient's reporting of MAD-related adverse events indicated that treatment was generally well tolerated, with a low burden of side effects (Table E5).

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DISCUSSION

Our findings confirm that MJM monitoring is an accurate tool for diagnosing OSA and determining disease severity. Notably, this study demonstrated, for the first time to our knowledge, the excellent performance of MJM automated analysis in home-based monitoring of MAD titration. Overall, measurement bias was consistent with previously reported LOAs of other FDA approved machine learning-based sleep test solutions (23-26). Home sleep testing with MJM monitoring allowed effective visualization of the trajectories of AHI and improvements of OSA symptoms throughout MAD therapy.

At the end of the MAD titration process, the AHI measured was similar between manual PG scoring and MJM automated analysis recorded the same night at a sleep clinic. These findings show that the reliability of MJM analysis is not impacted in individuals using oral appliances protruding the mandible forward. The MJM analysis replicated the same AHI distribution as determined by PG and captured the global trend of AHI changes with a high level of agreement. In addition to providing accurate data on the change in AHI between two time points (as obtained using PSG and PG), at-home MJM monitoring provides the opportunity for continuous monitoring of a progressive AHI response, allowing real-time adjustment of mandibular protrusion, ensuring that the MAD is optimized for each individual (9,27).

The present study also recorded enhancements in OSA symptoms with MAD therapy, encompassing improvements in sleep quality, reduced snoring, decreased morning fatigue, alleviated headaches, diminished dry mouth, and reduced daytime sleepiness. Additionally, MAD treatment demonstrated good tolerability. While gathered through specific visits or calls, in clinical application, this data could be acquired using the patient app of the MJM

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monitoring system. This approach would enable the collection of pertinent data and the seamless transmission of information to the clinician.

The accuracy of MJM monitoring for OSA diagnosis has previously been validated against PSG both in the sleep laboratory and at home (11,15). However, there are limited data on whether this accuracy compared with PSG/PG is preserved during MAD therapy. Only one previous study has investigated the use of MJM analysis to determine the effectiveness of oral appliance therapy in OSA (28). That study used a different MAD, but also successfully used MJM analysis to document the reduction in AHI during MAD therapy.

The sensitivity of the MJM monitoring technology is due to two important factors. Firstly, the bio-signal itself is highly robust and well-preserved, even during rapid eye movement sleep, due to the crucial leverage role that the lower jaw plays in maintaining pharyngeal patency. This ensures accurate and consistent data collection. Secondly, the utilization of inertial units in the capturing technology contributes to its robustness. These units are extensively used in fields like aviation and smartphones, highlighting their proven reliability and suitability for precise data acquisition in the scope of MJM technology.

The determination of the optimal level of mandibular advancement is currently not standardized. However, a potential approach to fine-tuning mandibular advancement involves monitoring both the AHI and subjective OSA symptoms during treatment. Although this approach has been explored, previous studies have not specifically examined individual responses at home in relation to the titration level as a percentage of the maximal protrusion (29). Some success has been reported with the use of at-home PG, with a ≥50% decrease in AHI reported in 72% of patients (26/36) after only minimal advancement (30). In the present study, we observed a similar optimal improvement rate of 50.5% right from the initial advancement level, and a cumulative normalization rate (AHI ≤ 5) as the protrusion

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level increased. These results demonstrate the benefits of real-time treatment monitoring process at home.

A cost-effective digital medicine solution with minimal technical and human resource requirements, enabling home monitoring over multiple nights, along with the collection of patient-reported outcome measures (PROMs) data, could offer a convenient approach for both clinical practice and research. Providing patients with devices in advance and getting results via a digital platform within minutes of the test being done would streamline the process, reducing the need for extensive in-person visits while significantly enhancing the capture of objective data on MAD effectiveness. This approach could effectively address challenges related to sleep laboratory capacity, which particularly worsened during the COVID-19 pandemic, and provide a valuable resource for individuals living in remote and isolated areas with limited access to in-laboratory PSG services. Local healthcare providers in these regions could easily adopt the MJM monitoring at home, which would be a significant advancement in making OSA management more accessible.

In addition, personalized titration by remotely monitoring both clinical symptoms and MJM would allow the prescription of the minimal level of advancement that is associated with sufficient reduction in AHI, thus limiting the potential side effects associated with the use of oral appliances. By adopting such an approach and using a lower level of mandibular advancement, the potential risk of inducing discomfort in the temporomandibular structures could be reduced (31). This is highly relevant given that the AASM guidelines acknowledge the development of temporomandibular disorders as the primary reason for discontinuing MAD therapy (32). There is also potential for such an approach to improve treatment compliance.

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Given the constraints of our observational study, our findings support the utility of MJM analysis as a monitoring tool but could not establish a causal link with treatment efficacy. Nonetheless, these findings suggest that at-home MJM analysis is valuable for remote MAD titration optimization.

Simplifying the MAD titration procedure remains a significant unmet requirement that restricts the broader adoption of oral appliance therapy. The efficacy of this therapeutic strategy is currently largely unpredictable before titration. Respiratory/sleep physicians frequently overlook oral appliance therapy as a viable option due to the intricate nature of the multidisciplinary care pathway, necessitating them to closely collaborate with dental specialists for comprehensive patient management. The use of MJM monitoring alongside digital medicine strategies could simplify this process. In addition, there is a need to define better the roles of stakeholders in MAD titration and follow-up to avoid inefficiency and redundancy in both the management pathway and reimbursement models. The development of multidisciplinary digital medicine platforms shared between dentists and sleep specialists might represent a step forward for easy access, better therapy implementation, and optimized treatment effectiveness (both in terms of objective data and PROMs).

Future studies should explore the long-term efficacy, the impact on the titration time, and cost-effectiveness of the MJM-based digital medicine approach compared with traditional MAD titration methods.

Conclusions

The results of this study showed the effectiveness and reliability of MJM monitoring coupled with an automated analysis by machine learning as a digital solution for MAD titration. The

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MJM-based method demonstrated a strong agreement with conventional in-laboratory PSG and PG in estimating AHI and evaluating the MAD treatment effect. Furthermore, the results of at-home MJM analysis revealed its potential for remote monitoring and optimization of MAD titration. Coupled with digital surveys, its capability would include continuous monitoring of the evolving AHI response and OSA-related symptoms, enabling real-time mandibular protrusion adjustments to ensure the MAD is tailored optimally to each patient. These findings help overcome several significant obstacles to the widespread clinical integration of MAD therapy for OSA. They also endorse the utilization of MJM automated analysis as a valuable tool to enhance accessibility to MAD therapy, improve treatment effectiveness, and patient outcomes.

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FIGURE LEGENDS

Figure 1 Study flowchart. MAD = mandibular advancement device; PG = polygraphy; PSG = polysomnography; SP = starting point of MAD titration; T1 = titration 1; T2 = titration 2.

Figure 2. Agreement between polysomnography (PSG)/polygraphy (PG) and mandibular jaw movement (MJM) automated analysis for estimation of the apnea-hypopnea index (AHI). For each plot: the x-axis represents the reference scale for AHI estimated by in-laboratory PSG (baseline) or in-laboratory PG (final control), and the y-axis represents the scale of measurement bias between MJM analysis and PSG or PG. Each point on the scatter plot represents an individual patient; the three horizontal dotted lines indicate the median value, the upper (95^{th} percentile) and lower (5^{th} percentile) limits of the measurement bias. The density curves on the upper panel represent the distribution of MJM-derived AHI (red) and PSG/PG derived AHI (blue). The vertical density curve on the right represents the distribution of measurement bias. MAD = mandibular advancement device.

Figure 3. Apnea-hypopnea index (AHI) distribution before and after mandibular advancement device therapy based on polysomnography/polygraphy (PSG/PG) or mandibular jaw movement (MJM) automated analysis. The figure consists of two layers: the front layer shows the distribution of AHI values at baseline and the end of study. The larger dots indicate the median AHI value at each time point and the bold line connecting these dots indicates the trend of AHI change at the population level. In the background, a combination of dots and line plots shows individual changes in AHI from baseline to the end of treatment. For all graphical elements, blue indicates AHI assessment by PSG/PG and red indicates AHI assessment using MJM automated analysis.

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Figure 4. Change in the apnea-hypopnea index (AHI) during mandibular advancement device (MAD) therapy at home. This figure has the same structure as Figure 3. The x-axis shows the baseline and the three ascending levels of MAD protrusion: initial protrusion was 60.00 ± 0.00%, intermediate protrusion was 68.15 ± 1.66 %, and final protrusion was the final effective protrusion level achieved (76.56 ± 3.67%) of maximum active protrusion.

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TABLES

Table 1. Demographic and clinical characteristics of the study population, and polysomnography findings at baseline

Parameters	**Participants (n=135)**
Age, years	48.8 (33.7; 64.1)
Male sex, n (%)	100 (74)
Body mass index, kg/m^2	27.4 (21.5; 33.3)
Neck circumference, cm	40.0 (30.0; 44.0)
ESS score	11 (4; 19)
OSA subgroup, n (%)	
Obstructive RDI <5/h with snoring	2 (1)
Obstructive RDI 5–15/h with symptoms	21 (16)
Positional OSA	32 (24)
OSA severity, n (%)	
Mild (AHI 5 to <15/h)	13 (10)
Moderate (AHI 15 to <30/h)	75 (56)
Severe (AHI ≥30/h)	47 (34)
Symptoms, n (%)	
Snoring	120 (89)
Witnessed apneas	73 (54)
Morning headache	82 (61)
Morning fatigue	106 (79)
Fatigue during the day	110 (81)

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Insomnia	58 (51)
PSG data	
TST, h	7.1 (4.8; 8.7)
Sleep efficiency, %	72.3 (51.4; 91.5)
Arousal index, /h	27.1 (13.7; 49.2)
AHI, /h	24.6 (13.4; 58.0)
Supine AHI, /h	23.8 (8.8; 57.7)
Non-supine AHI, /h	19.7 (6.1; 57.7)
AHI during non-REM sleep, /h	18.0 (8.0; 41.0)
AHI during REM sleep, /h	19.1 (1.3; 49.5)
Obstructive AHI, /h	18.8 (6.2; 47.6)
Central AHI, /h	4.5 (0.2; 19.9)
RDI, /h	29.4 (15.4; 59.4)
Obstructive RDI, /h	23.7 (8.4; 49.1)
RERA index, /h	2.8 (0.3; 9.9)
ODI, /h	17.2 (3.5; 58.4)

Values are median (5^{th} percentile; 95^{th} percentile) or number of participants (%).

Definition of abbreviations: AHI = apnea-hypopnea index; ESS = Epworth Sleepiness Scale; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; PSG = polysomnography; RDI = respiratory disturbance index; REM = rapid eye movement; RERA = respiratory effort-related arousal; TST = total sleep time.

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Table 2. Change in the average apnea-hypopnea index from baseline to end of titration based on different evaluation methods

Evaluation method		n	Change in AHI versus baseline (95% CI)		
Baseline	**End of titration**		**Absolute, /h**	**Relative, %**	**P-value**
In-lab PSG	In-lab PG	105	–15.6 (–15.6; –15.5)	–55.6 (–55.8, –55.5)	<0.0001
In-lab PSG	In-lab PG	93	–16.7 (–16.7; –16.6)	–59.6 (–59.8; –59.5)	<0.0001
HST MJM	HST MJM	93	–13.0 (–15.5; –10.4)	–59.7 (–67.4; –50.2)	<0.0001
In-lab PSG	In-lab MJM	105	–15.2 (–18.0; –12.4)	–54.2 (–59.6; –48.2)	<0.0001
In-lab PSG	In-lab MJM	93	–16.6 (–20.1; –13.1)	–59.2 (–65.2; –52.2)	<0.0001

Definition of abbreviations: AHI = apnea-hypopnea index; CI = confidence interval; HST = home sleep test; In-lab = in-laboratory; MJM = automated analysis of mandibular jaw movements; PG = polygraphy; PSG = polysomnography.

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Table 3. Impact of mandibular advancement device therapy on patient-reported outcome measures

Measure	Baseline	End of titration	Change from baseline (95% CI)		
			Absolute, /h	**Relative, %**	**P-value**
Global satisfaction with sleep quality*	3.4 ± 1.7	6.2 ± 2.0	2.2 (2.0; 2.5)	62.3 (52.1; 73.3)	<0.0001
Snoring†	7.9 ± 2.2	2.2 ± 2.0	–3.8 (–4.0; –3.5)	–60.4 [–63.4; –57.3)	<0.0001
Morning fatigue†	6.1 ± 2.1	4.4 ± 2.2	–1.2 (–1.7; –0.7)	–21.5 (–29.1; –13.1)	<0.0001
Headache†	3.2 ± 2.2	0.8 ± 1.8	–0.9 (–1.1; –0.7)	–22.1 (–26.7; –17.1)	<0.0001
Dry mouth†	4.6 ± 2.7	2.2 ± 2.0	–2.1 (–2.4; –1.7)	–44.3 (–49.4; –38.7)	<0.0001
ESS score‡	11.1 ± 4.3	8.5 ± 4.4	–2.7 (–3.4; –2.0)	–24.5 (–30.0; –18.6)	<0.0001
Pichot Fatigue Scale score‡	12.3 ± 6.7	8.0 ± 7.4	–3.2 (–4.5; –2.0)	–27.3 (–35.5; –18.0)	<0.0001

Baseline and end of titration values are mean ± standard deviation. *Definition of abbreviations:* CI = confidence interval; ESS = Epworth Sleepiness Scale.

*Rated on a scale from 0 to 10, where higher scores indicate higher levels of satisfaction.

†Self-reported OSA symptoms were rated on a scale from 0 to 10 where a higher score indicates a higher rate of that symptom.

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‡The ESS and Pichot Fatigue Scale were scored from 0–24 and 0–32, respectively; data were converted into a standard continuous scale to be compatible with the statistical inference which implied a generalized linear mixed model with beta-distribution.

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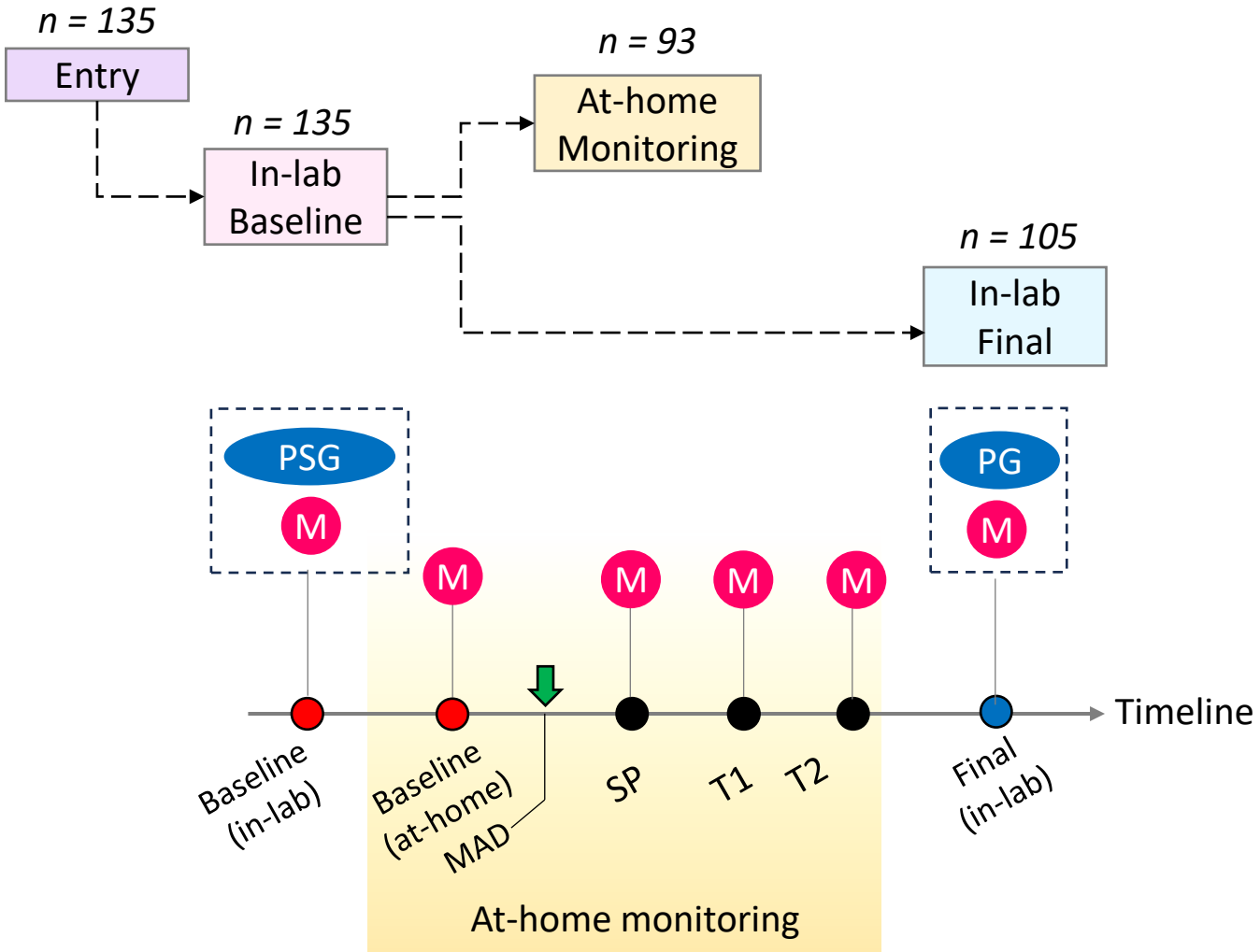

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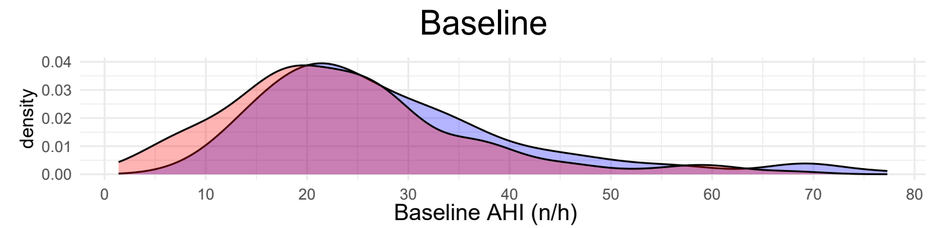

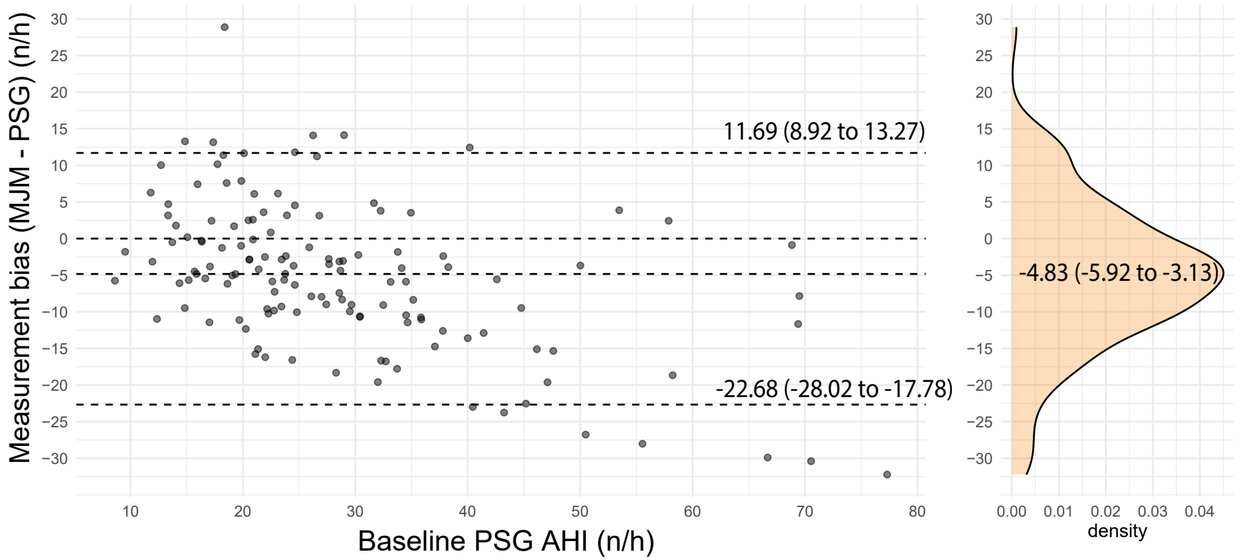

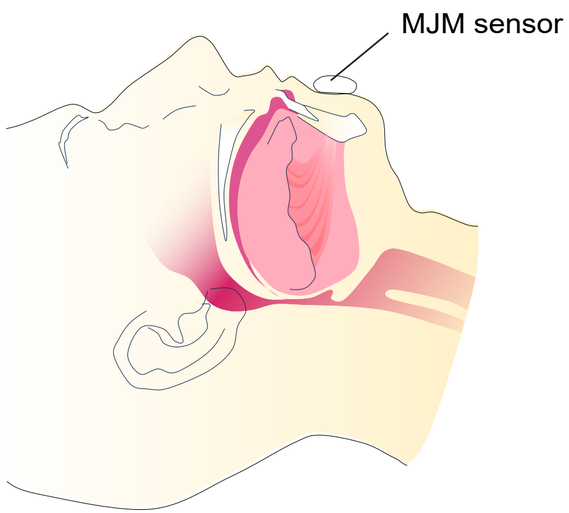

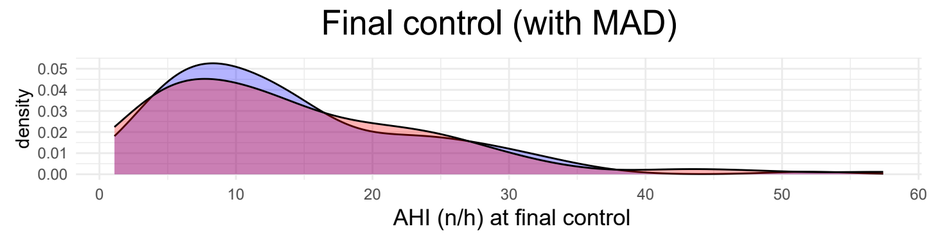

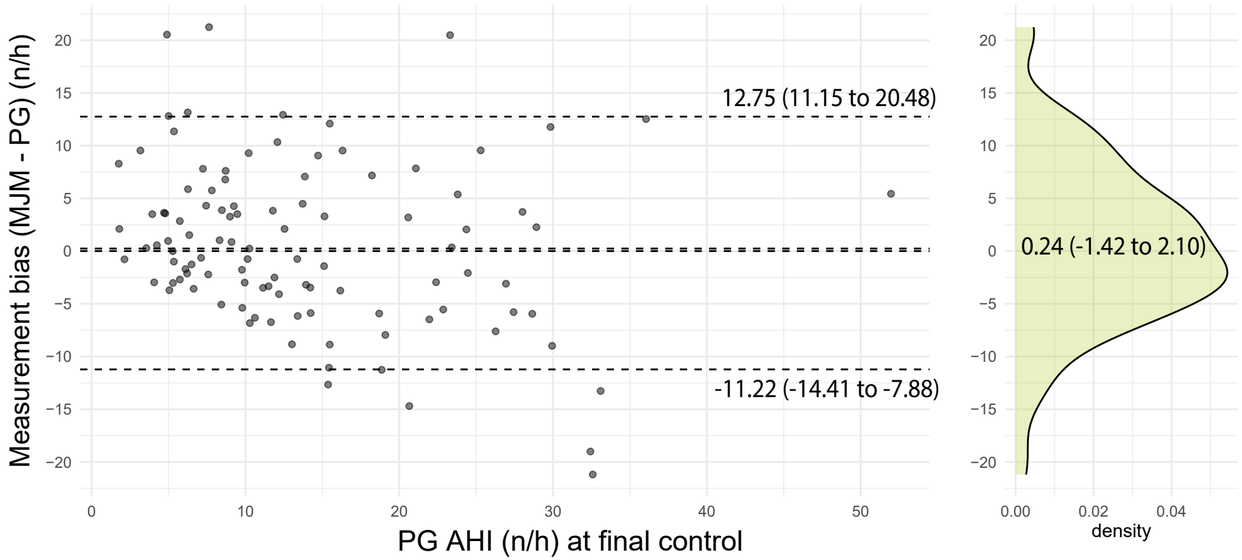

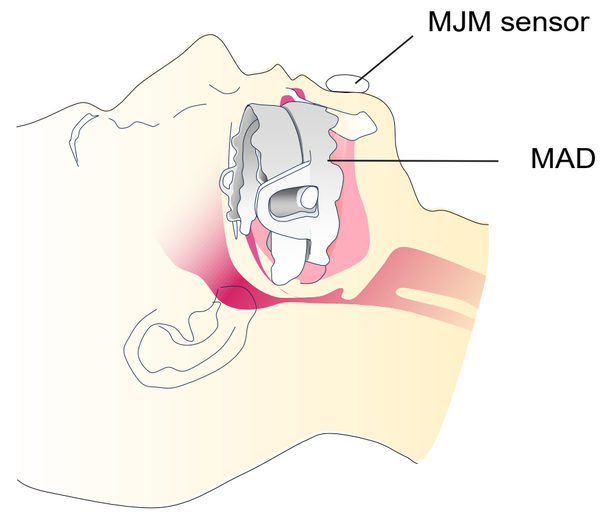

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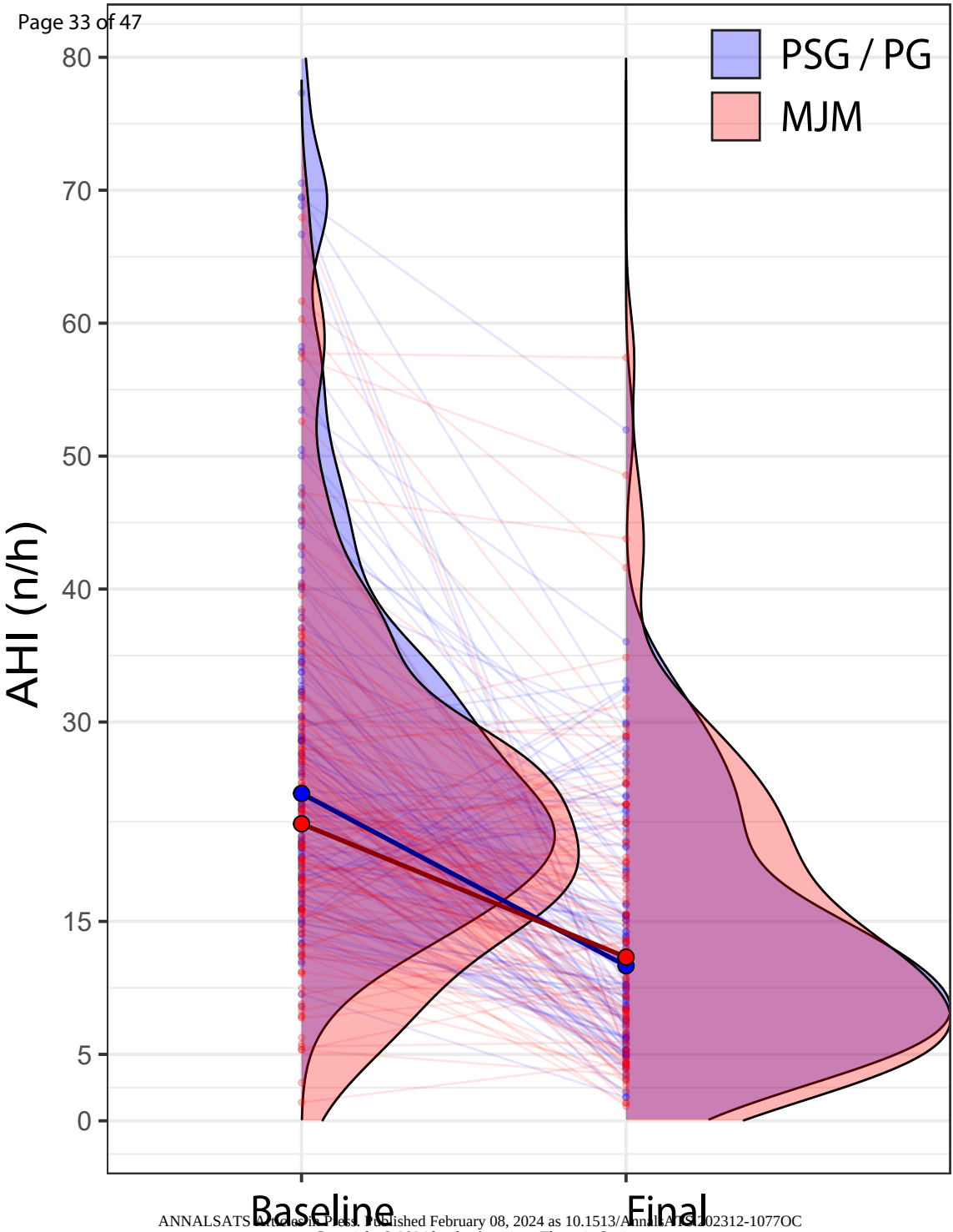

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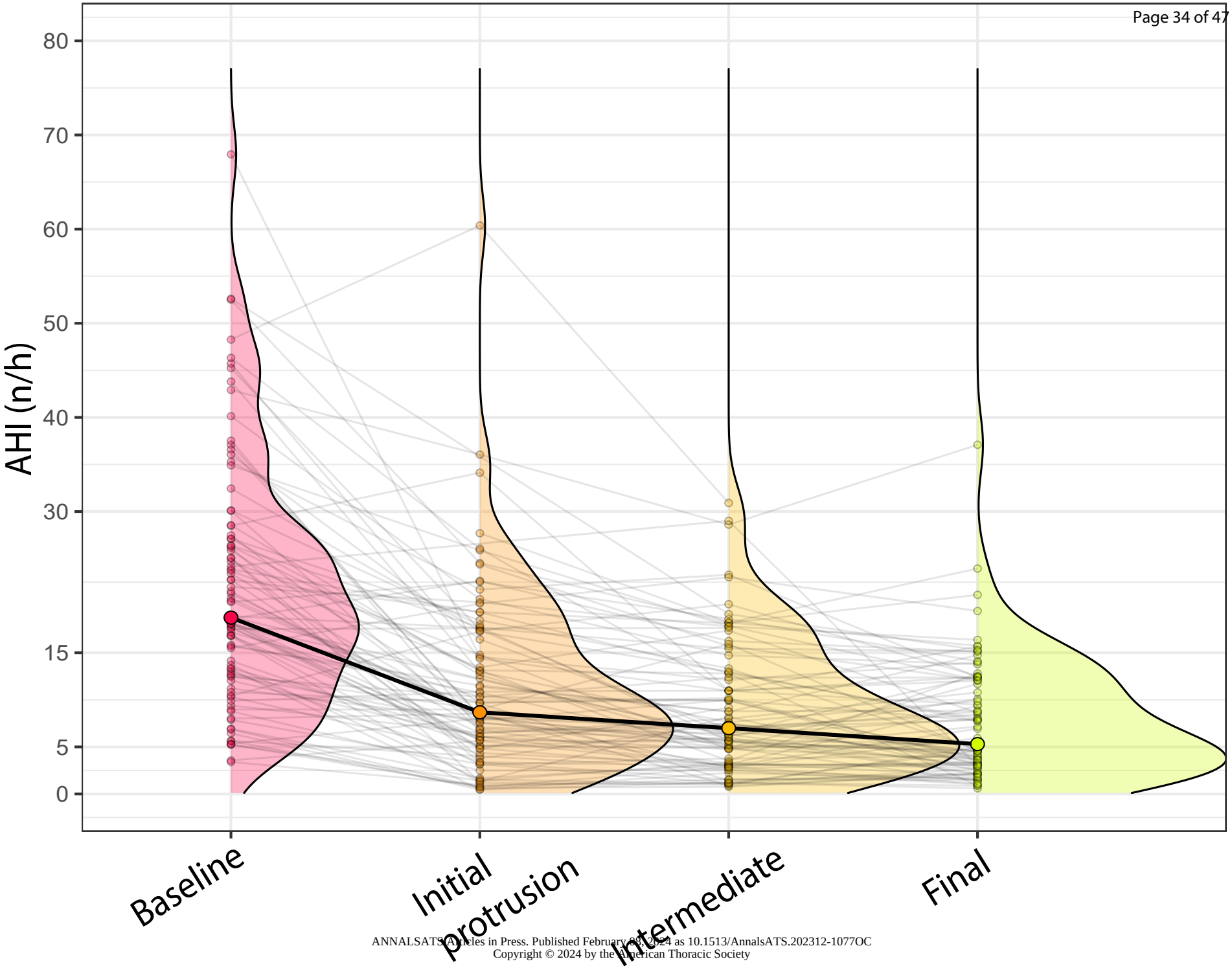

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Online Data Supplement

Mandibular Jaw Movement Automated Analysis for Oral Appliance Monitoring in Obstructive Sleep Apnea: A Prospective Cohort Study

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SUPPLEMENTARY METHODS

Mandibular advancement device

The mandibular advancement device (MAD) used in this study (NOA; OrthoApnea, Malaga, Spain) is a titratable two-piece device, crafted with interconnected vertical branches. It incorporates a maxillary arch and diverse mandibular bites. The latter consist of a series of lower splints, which emulate protrusive lines, thereby allowing the individual to gradually achieve an effective degree of advancement. This customized appliance was fabricated from polyamide-12 via 3D printing. The NOA device allows for lateral jaw movements without the need for rubber bands to secure mouth closure. Jaw protrusion is facilitated by preventing a jaw backward movement through a specific mortise (known as ‘CAM’) on the lower branch, which is dimensioned to accommodate the 'FOLLOWER' tenon printed on the upper bite.

Sunrise technology for mandibular jaw movement-based automated analysis

Mandibular jaw movements (MJM) were recorded using the Sunrise technology (Sunrise, Namur, Belgium) (1-3), a system composed of a coin-sized, single point of contact sensor placed on the patient’s chin between the inferior labial sulcus and the pogonion. The embedded inertial measurement unit of the sensor includes a gyroscope and an accelerometer and is controlled externally via a smartphone application. The gyroscope and accelerometer measure along their three axes (X, Y, Z) the rotational movement and position of the mandible, respectively. The rotational movement captured by the gyroscope is produced by rotation of the mandibular condyle in the temporo-mandibular joint.

At the end of a recording session, MJM data is automatically transferred to a cloud-based infrastructure for subsequent data analysis. The data processing is conducted using a dedicated machine-learning algorithm. This algorithm is designed to automatically identify sleep stages (awake, light/deep or rapid eye movement sleep) (1), obstructive, central and mixed apnea/hypopnea or

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respiratory effort-related arousal events (4), based on stereotypical MJM patterns. The combined outputs from the sleep stage and respiratory event classifiers allow for estimating the apnea hypopnea index (AHI).

Sample size estimation process

The sample size required for this study was estimated to optimize the accuracy of statistical inference for the two research questions: (1) validating the agreement between MJM monitoring and conventional polysomnography with respect to determination of the AHI; and (2) evaluating the efficiency of MJM monitoring for detecting a clinical response to MAD therapy.

For the first question, the aim of sample size estimation was to optimize the accuracy of statistical inference on limits of agreement (LOA) in a Bland-Altman analysis for AHI measurement bias. This was achieved using the estimation procedure developed by Lu et al (2016) (5), which is implemented to R via the blandPower package. The rationale of this estimation is that the agreement between two methods would be considered clinically acceptable if the 95% confidence interval (95% CI) for the LOA is within a pre-defined threshold. The estimation generated three parameters: μ and σ, which indicate the expected value and standard deviation of LOA, respectively, and a pre-defined clinical threshold.

A simulation of the required sample size for the AHI comparison was based on empirical pilot study data from 50 subjects. Based on the results of this simulation, it was determined that a sample of 90–100 participants would be sufficient to validate an absolute mean LOA of measurement bias for AHI ranging from 5/h to 14/h against the clinical acceptability threshold of 25 events/h, with 80% power and a type I error of 0.05 (Figure E1).

For the second question, the estimated sample size required to detect a significant change in the AHI during MAD therapy based on a mean relative change of 40% to 70% and a standard deviation for the absolute change in AHI of 4.5 to 14/h, compared with a baseline AHI of 10 to 80/h was determined. The estimation was based on Cohen's method for statistical inference using paired-samples t-test (6).

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This simulation also determined that a sample size of 90–100 would be required to provide 80% power with a type I error of 0.05 (Figure E2).

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SUPPLEMENTARY FIGURES

Figure E1. Simulation of sample size for statistical inference on limits of agreement for apnea-hypopnea index (AHI) measurement bias in Bland-Altman analysis.

This plot shows the relationship between statistical power (y-axis) of statistical inference on limits of agreement for AHI (varying from 5 to 14 units) and the sample size (x-axis).

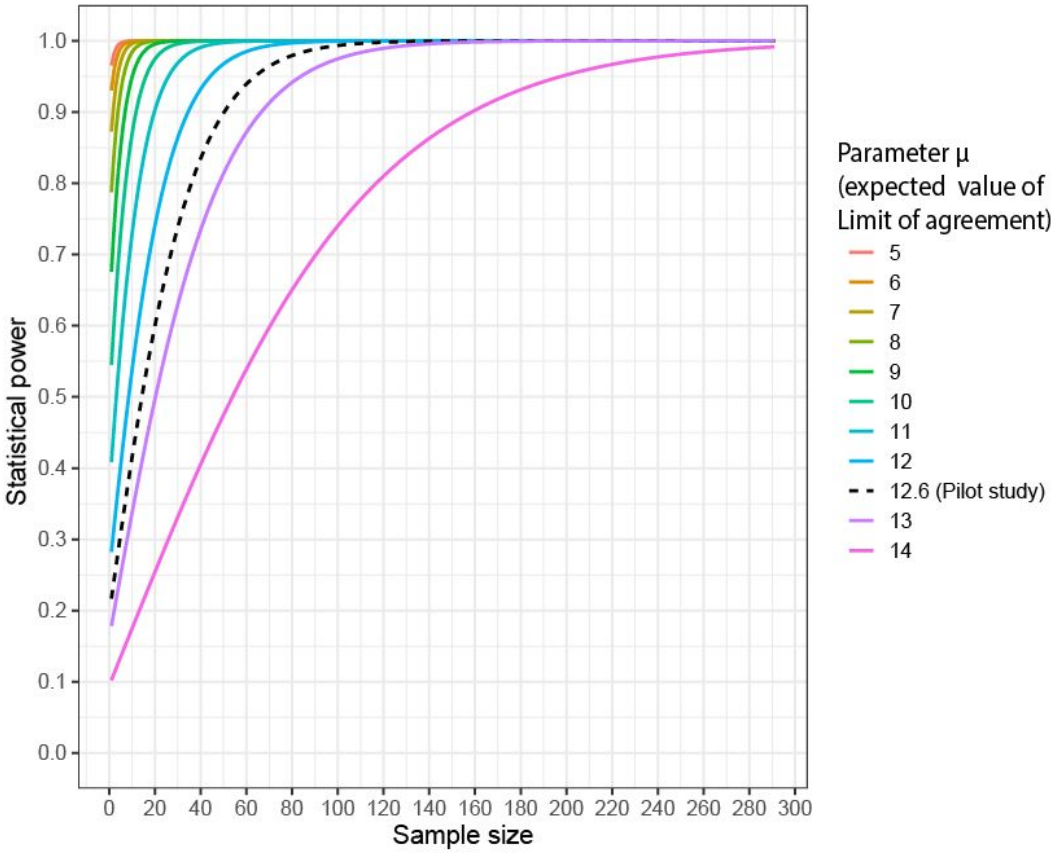

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Figure E2. Simulation of sample size for detecting a significant treatment effect on the apnea-hypopnea index (AHI).

These 3-dimenstional plots show the variation of minimum required sample size (vertical axis) as a function of the value of three other parameters: expected relative change in AHI from baseline, mean value of AHI at baseline (left panel) and standard deviation (SD) of AHI change (right panel).

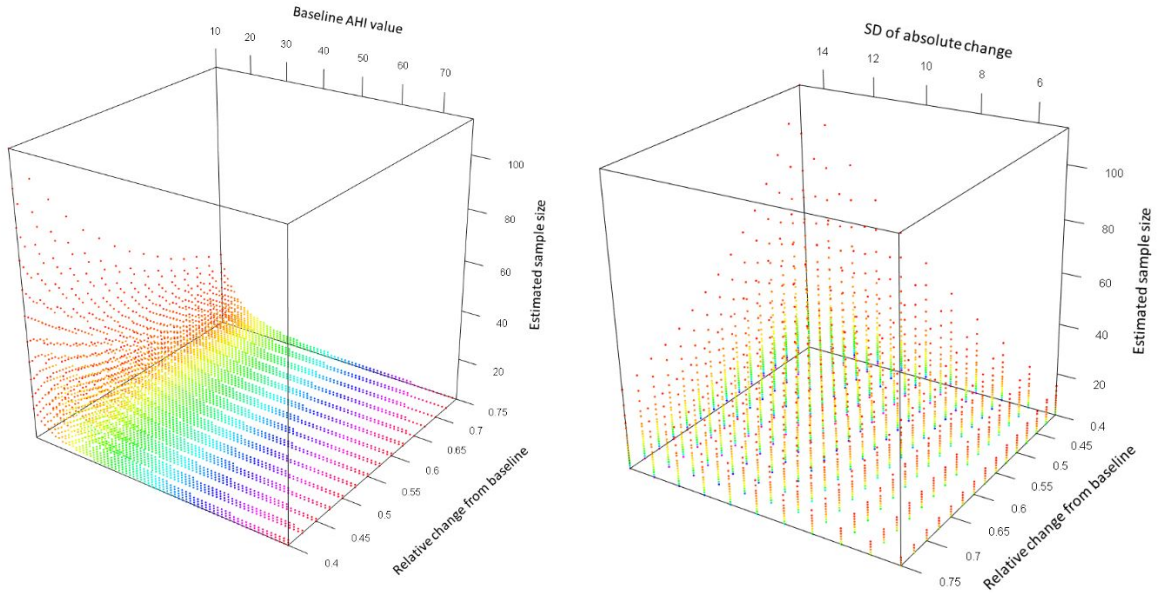

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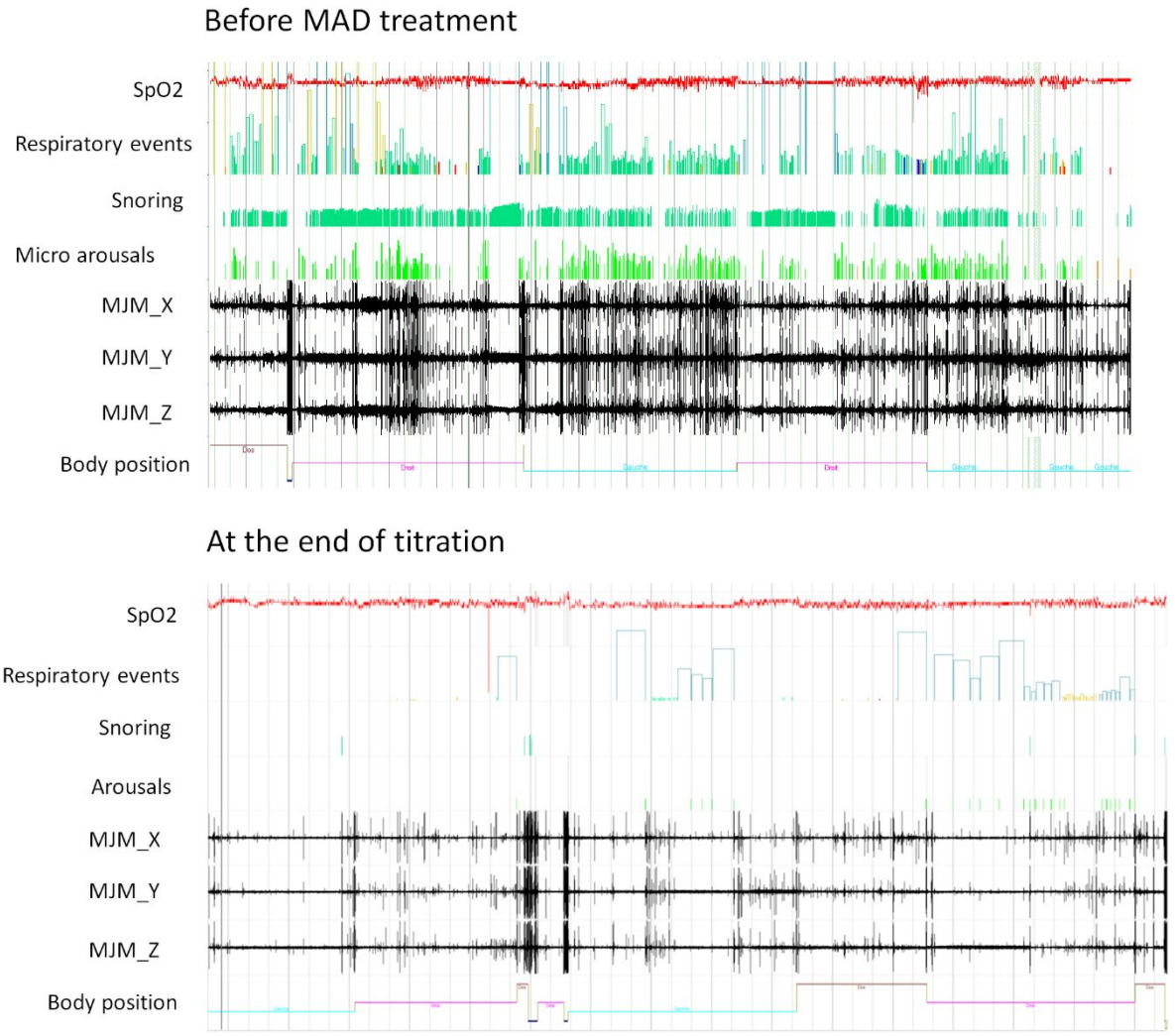
Figure E3. Visualization of the overnight gyroscopic signal from mandibular jaw movements (MJM) monitoring alongside manually scored data from conventional polysomnography/polygraphy, before and during mandibular advancement device (MAD) therapy.



Legend: Example of the PSG/PG integrated with MJM signal recording before MAD treatment (upper graph) and at the end of titration (lower graph). At the second row: the green vertical lines indicate a high occurring rate of respiratory events (mostly obstructive hypopneas) at the baseline, which has been significantly reduced at the end of MAD titration. SpO2 = oxygen saturation, MJM X,Y,Z: MJM signal captured by the tri-axial sensor.

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SUPPLEMENTARY TABLES

Table E1. Incremental protrusion level during mandibular advancement device (MAD) therapy

MAD level (% of maximum voluntary protrusion)	**Initial**	**Intermediate**	**Final**
Median (5^{th} - 95^{th} percentile)	60.00 (60.00; 60.00)	67.69 (65.99; 71.11)	76.03 (71.87; 82.22)

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Table E2: Evaluation of MAD treatment effect on the rate of apnea-hypopnea events with adjustment for variation of TST

Evaluation method		n	Change in number of apnea/hypopnea events versus baseline (95% CI)*	
Baseline	**End of titration**		**Relative, %**	**P-value**
In-lab PSG	In-lab PG	105	-49.94 (-56.34 to -42.60)	<0.0001
In-lab PSG	In-lab PG	93	-54.83 (-61.97 to -46.35)	<0.0001
HST MJM	HST MJM	93	-61.23 (-68.87 to -51.70)	<0.0001
In-lab PSG	In-lab MJM	105	-50.75 (-57.51 to -42.92)	<0.0001
In-lab PSG	In-lab MJM	93	-55.14 (-62.99 to -45.61)	<0.0001

Note : statistical inference was based on a negative binomial GLMM regression that estimate the change in total number of apnea-hypopnea events under MAD treatment. The estimated treatment effect was adjusted for total sleep time (TST) as a covariate.

CI = confidence interval; HST = home sleep test; In-lab = in-laboratory; MJM = automated analysis of mandibular jaw movements; PG = polygraphy; PSG = polysomnography.

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Table E3. Change in the apnea-hypopnea index at different time points during home-based follow-up

	Estimated change in AHI (95% CI)*		
	Absolute, /h	**Relative, %**	**P-value**
Initial protrusion vs. baseline	–10.3 (–12.5; –8.2)	–47.7 (–54.2; –40.1)	<0.0001
Intermediate protrusion vs. baseline	–12.7 (–15.2; –10.3)	–58.6 (–64.4; –51.9)	<0.0001
Final protrusion vs. baseline	–13.0 (–15.5; –10.4)	–59.7 (–67.4; –50.2)	<0.0001
Intermediate vs. initial protrusion	–2.4 (–3.6; –1.1)	–21.0 (–29.5; –11.5)	0.0019
Final vs. intermediate protrusion	–0.2 (–1.7; 1.2)	–2.6 (–1.8; 15.3)	NS
Final vs. initial protrusion	–2.6 (–4.0; –1.3)	–23.1 (–33.7; –10.7)	0.0005

*Marginal effect estimation and statistical inference were based on a generalized estimating equation model with Gamma distribution. *Definition of abbreviations:* AHI = apnea-hypopnea index; CI = confidence interval.

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Table E4. Incremental improvements in snoring and the Epworth Sleepiness Scale score during home titration of mandibular advancement device therapy

	Mean change (95% CI)		
	Absolute, /h	**Relative, %**	**P-value**
Snoring*			
Initial protrusion vs. baseline	–2.4 (–2.9; –1.9)	–38.6 (–44.8; –31.6)	<0.001
Intermediate vs. initial protrusion	–1.0 (–1.4; –0.6)	–26.4 (–35.7; –15.7)	<0.001
Maximum vs. intermediate protrusion	–0.6 (–1.0; –0.1)	–19.6 (–31.6; –5.4)	0.008
Final vs. maximum protrusion	–0.4 (–1.6; 0.9)	–15.7 (–55.6; 59.9)	0.571
ESS score†			
Initial protrusion vs. baseline	–1.9 (–3.0;–0.8)	–16.8 (–25.1; –7.6)	0.001
Intermediate vs. initial protrusion	–1.5 (–2.6;–0.5)	–16.2 (–25.8; –5.3)	0.004
Maximum vs. intermediate protrusion	–0.9 (–1.9; 0.2)	–10.9 (–22.4; 2.2)	0.097
Final vs. maximum protrusion	0.6 (–0.4; 1.7)	9.1 (–4.9; 25.1)	0.212

Definition of abbreviations: AHI = apnea-hypopnea index; CI = confidence interval; ESS = Epworth Sleepiness Scale.

*Self-reported snoring was rated on a scale from 0 to 10, where a higher score indicates more frequent snoring.

†The ESS score was rated on a scale from 0 to 24, where higher scores indicate greater levels of daytime sleepiness.

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Table E5. Tolerability of mandibular advancement device therapy based on data at the end of titration

Adverse events	Tolerability score*
Temporo-mandibular joint tenderness	2.58 ± 1.96
Occlusal contact alteration	3.14 ± 2.18
Masticatory spasms	2.83 ± 2.11
Toothache	3.37 ± 2.30
Masticatory muscles tenderness	2.95 ± 2.12
Mastication alteration	2.65 ± 2.03

Values are mean ± standard deviation.

*Participants rated the extent of side effects during mandibular advancement device therapy on a scale from 0 to 10, where 0 = none/not problematic and 10 = extremely problematic.

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