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SCIENTIFIC INVESTIGATIONS

Development of a physiological-based model that uses standard polysomnography and clinical data to predict oral appliance treatment outcomes in obstructive sleep apnea

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Study Objectives: Oral appliance (OA) therapy is a well-tolerated alternative to continuous positive airway pressure. However, it is less efficacious. A major unresolved clinical challenge is the inability to accurately predict who will respond to OA therapy. We recently developed a model to estimate obstructive sleep apnea pathophysiological endotypes. This study aimed to apply this physiological-based model to predict OA treatment responses.

Methods: Sixty-two men and women with obstructive sleep apnea (aged 29–71 years) were studied to investigate the efficacy of a novel OA device. An in-laboratory diagnostic followed by an OA treatment efficacy polysomnography were performed. Seven polysomnography variables from the diagnostic study plus age and body mass index were included in our machine-learning-based model to predict OA therapy response according to standard apnea-hypopnea index (AHI) definitions. Initially, the model was trained on data from the first 45 participants using 10-fold cross-validation. A blinded independent validation was then performed for the remaining 17 participants.

Results: Mean accuracy of the trained model to predict OA therapy responders vs nonresponders (AHI < 5 events/h) using 10-fold cross-validation was 91% ± 8%. In the independent blinded validation, 100% (AHI < 5 events/h); 59% (AHI < 10 events/h); 71% (50% reduction in AHI); and 82% (50% reduction in AHI to < 20 events/h) of the 17 participants were correctly classified for each of the treatment outcome definitions respectively.

Conclusions: While further evaluation in larger clinical data sets is required, these findings highlight the potential to use routinely collected sleep study and clinical data with machine learning–based approaches underpinned by obstructive sleep apnea endotype concepts to help predict treatment outcomes to OA therapy for people with obstructive sleep apnea.

Keywords: dental sleep medicine, sleep-disordered breathing, pathophysiology, endotype, precision medicine, mandibular advancement device

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Accurate prediction of which obstructive sleep apnea patients will respond to oral appliance therapy remains a major clinical challenge. This study aimed to develop a physiological-based model underpinned by obstructive sleep apnea endotype concepts to predict oral appliance treatment responses.

Study Impact: The current findings describe a novel physiological-based approach to help predict oral appliance therapy outcomes for people with obstructive sleep apnea. This new approach has considerable translational potential to help increase oral appliance treatment prediction accuracy beyond the current 50% mark using readily available information from a standard sleep study report and clinical data.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common, chronic sleep-related respiratory disorder.[1] The characteristic breathing disturbances which define OSA cause intermittent hypoxia and sleep fragmentation. Untreated OSA is associated with a range of adverse health and safety outcomes including cardiometabolic disease and increased risk of traffic accidents.[2,3]

Continuous positive airway pressure (CPAP) is the first-line therapy for OSA. It is highly efficacious but is often poorly tolerated.[4,5] Oral appliance therapy to advance the mandible is a well-tolerated alternative to CPAP.[6] However, oral appliance therapy is less efficacious than CPAP.[7] Indeed, approximately 50% of patients have an incomplete or no therapeutic response with oral appliance therapy depending on the definition of successful treatment outcome used.[8] These incompletely treated and untreated patients remain at risk of adverse health and safety outcomes. In addition, while the overall health benefits of oral appliance therapy are comparable to CPAP,[7] the time (ie, multiple dental and specialist visits) and cost involved with oral appliance therapy can be substantial[9] and often follow a failed trial of CPAP. Thus, it would be desirable to accurately identify individuals who are likely to respond favorably to oral appliance therapy, and vice versa, prospectively.[10] Accordingly, a major unresolved clinical priority is to develop clinically deployable tools to help predict who will respond to oral appliance therapy.

Recent advances in knowledge of the pathophysiology of OSA have identified 4 important endotypes or "treatable traits."[11–14] Evidence from proof-of-concept physiology studies indicates that OSA endotypes differ in patients who do vs do not respond to non-CPAP therapies such as upper-airway surgery, hypoglossal nerve stimulation, and emerging pharmacotherapies.[13,15–18] Indeed, OSA endotype characteristics are different in responders vs nonresponders to oral appliance therapy.[19–21] Accordingly, estimation of OSA endotypes may help predict which patients will respond to different non-CPAP therapies including oral appliances.[22–24] However, prior OSA endotyping work to predict oral appliance treatment responses has relied on complex signal processing approaches[19–21] that require specialized expertise to conduct and thus are not currently available for clinical prediction at scale. With these limitations in mind, we have recently developed a prediction model to estimate the 4 key OSA endotypes that uses standard clinical and polysomnography data routinely collected from a diagnostic sleep study.[14] This study aimed to apply this physiology-based model to predict oral appliance treatment responses.

METHODS

Participants

Sixty-two men and women with OSA (apnea-hypopnea index [AHI] > 5 events/h sleep) were studied as part of a larger trial to investigate the role of OSA endotypes on the efficacy of a novel oral appliance (ACTRN12618001995268). All participants were recommended for oral appliance therapy by their treating sleep physician and provided informed written consent to participate. The study was approved by the South Eastern Sydney Local Health District Human Research Ethics Committee (18/047 HREC/18/POWH/124).

Study design

Initially, in-laboratory overnight polysomnography was performed to quantify OSA severity and confirm eligibility. Eligible participants (AHI > 5 events/h) referred into the trial by their sleep physician were then assessed by the study dentist for dental suitability for oral appliance therapy. If deemed medically suitable, dental impressions were taken at the initial dental consult and a custom-built oral appliance with a built-in oral airway to allow for oral breathing if required was manufactured (O_2Vent, Oventus Medical, Indooroopilly, Queensland, Australia). Following gradual titration to maximal tolerable mandibular advancement and acclimatization supervised by the study dentist over approximately 1–3 months, participants returned for in-laboratory overnight polysomnography to assess oral appliance treatment efficacy.

Overnight polysomnography

Electroencephalograms (F3, F4, C3, C4, O1, and O2, referenced to A1–A2), electrooculograms, surface submental and leg electromyograms, pulse oximetry, body position, nasal pressure flow, oronasal thermistor flow, thoracic and abdominal respiratory bands, and snore sound were measured. Data were acquired using an Alice 6 LDx diagnostic sleep system and Sleepware G3, version 3.7.4 data acquisition software (Phillips Respironics, Murrysville, PA).

Polysomnography data were scored for sleep and respiratory events according to American Academy of Sleep Medicine criteria.[25] Hypopneas were defined as a ≥ 30% reduction in peak flow from baseline for ≥ 10 seconds followed by either a ≥ 3% reduction in blood oxygen saturation or a cortical arousal. Scoring of sleep studies was performed by a board-registered polysomnographic technologist blinded to the condition.

Responder definitions

Responders to oral appliance therapy were defined according to 4 definitions: (1) treatment AHI < 5 events/h, (2) treatment AHI < 10 events/h, (3) ≥ 50% reduction in baseline AHI, and (4) ≥ 50% reduction in baseline AHI to < 20 events/h. We selected these 4 commonly used responder definitions to enable comprehensive clinical evaluation of the performance characteristics of the model and to allow for comparison with prior literature, including across treatment modalities (eg, definition 4 is commonly used in the surgical literature).[26,27]

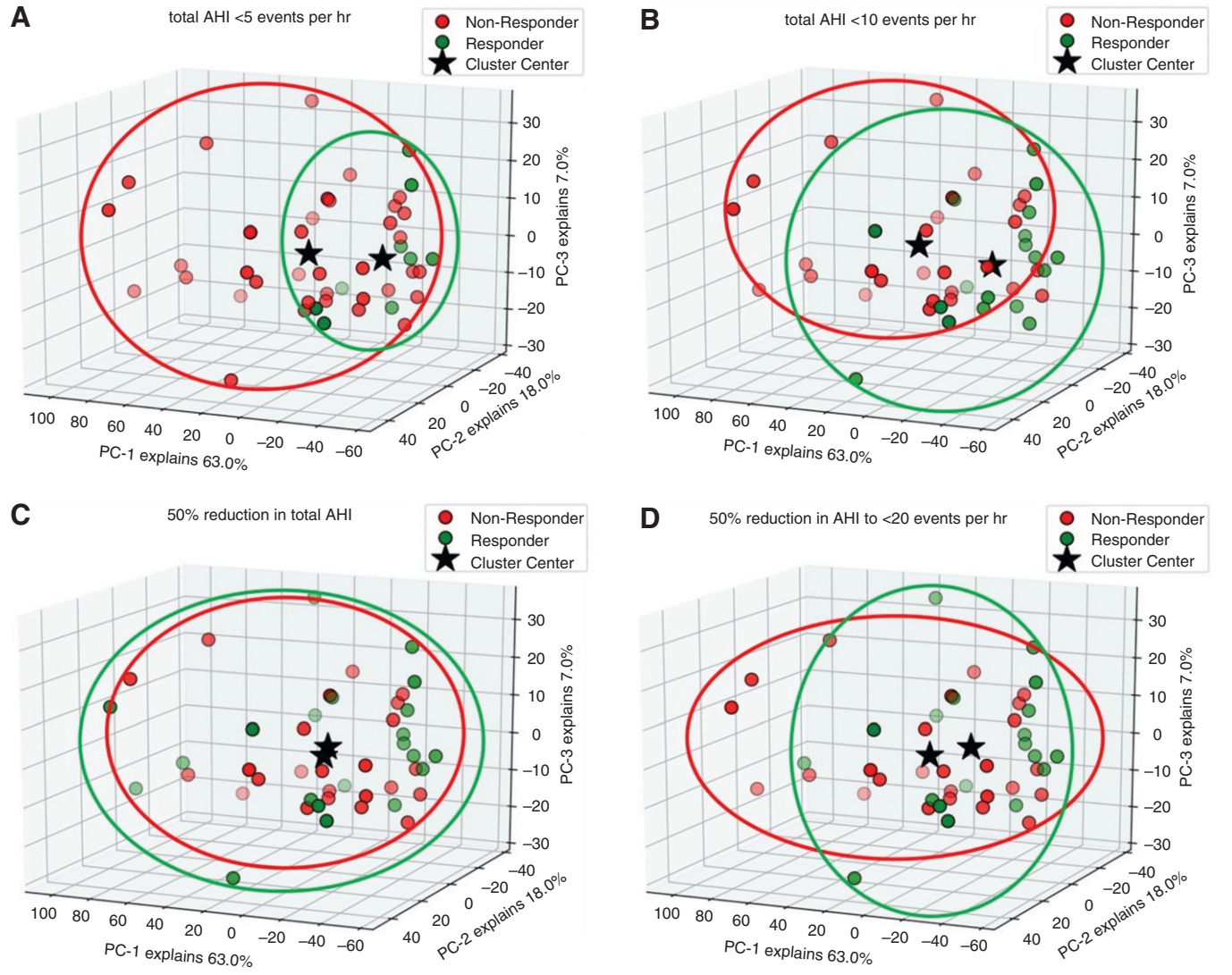
Predictive algorithm and analysis approach

In this study we used our recently developed prediction model to estimate the 4 key OSA endotypes[14] and refined it to predict treatment responses to oral appliance therapy. Further methodological details of the model, which consists of unsupervised multivariate principal component analyses (step 1) and data-driven supervised machine learning (decision tree learner, step 2), are provided in the original publication.[14] Briefly, in the current study, 7 standard polysomnography variables from the diagnostic study (total AHI, nadir estimated arterial blood oxygen saturation, arousal index, rapid eye movement sleep AHI, supine AHI, nonrapid eye movement sleep AHI, and the fraction of hypopneas:apneas) plus age and body mass index were included in our model to predict oral appliance therapy response according to the 4 AHI-based responder definitions that we selected.

In step 1, principal component analysis was performed to identify the amount of information variation of the input variables along the projected orthogonal axes (**Figure 1**). This process removes the effect of highly correlated variables from a data set in an unsupervised manner to reduce the dimensions of the original data set (ie, to identify independent predictors). A high amount of information variation across the first 3 principal components indicates suitability for development of a supervised prediction classifier.

In step 2, 12 different supervised machine-learning classifiers suitable for prediction classification were employed to be trained with the same input data. The 12 modeling approaches used were nearest neighbors, support vector machine, Gaussian process, decision tree, random forest, perceptron neural net, Ada boosting, naïve Bayes, quadratic discriminant analysis, extremely randomized forest, gradient boosting, and logistic regression. Performance characteristics for each of these 12 prediction classifiers were compared for each of the 4 treatment definitions. The best-performing classifier was then selected in each case to optimize prediction accuracy. In addition, the decision tree learner was used to visually display the internal

Figure 1—Principal component analysis–based comparative cluster plots.



(A) highlights the data for treatment definitions according to an apnea-hypopnea index (AHI) < 5 events/h, **(B)** AHI < 10 events/h, **(C)** 50% reduction in AHI, and **(D)** 50% reduction in AHI to < 20 events/h on oral appliance therapy. Each of the dots represents an individual participant's position on the projected 3-dimensional scatter plots. Green dots and corresponding cluster boundaries indicate responders while red dots indicate nonresponders. The black stars highlight the cluster centers of the 2 clusters. AHI = apnea-hypopnea index.

workings/decisions of the model for each treatment definition to provide novel clinical and physiological insight of the entire data set (Figure 2).

Initially, the model was trained on data from the first 45 participants using 10-fold cross-validation. An independent validation was then performed for the remaining 17 participants. The validation data set was part of the original data set. However, these data were kept separate from the training and testing paradigm to allow for blinded validation. Our approach to train the model on data from approximately two-thirds of the participants and then perform validation on the remaining one-third was selected to optimize the amount of data available for training while still allowing sufficient data for robust independent, blinded validation. Performance accuracy is reported as mean ± standard deviation.

RESULTS

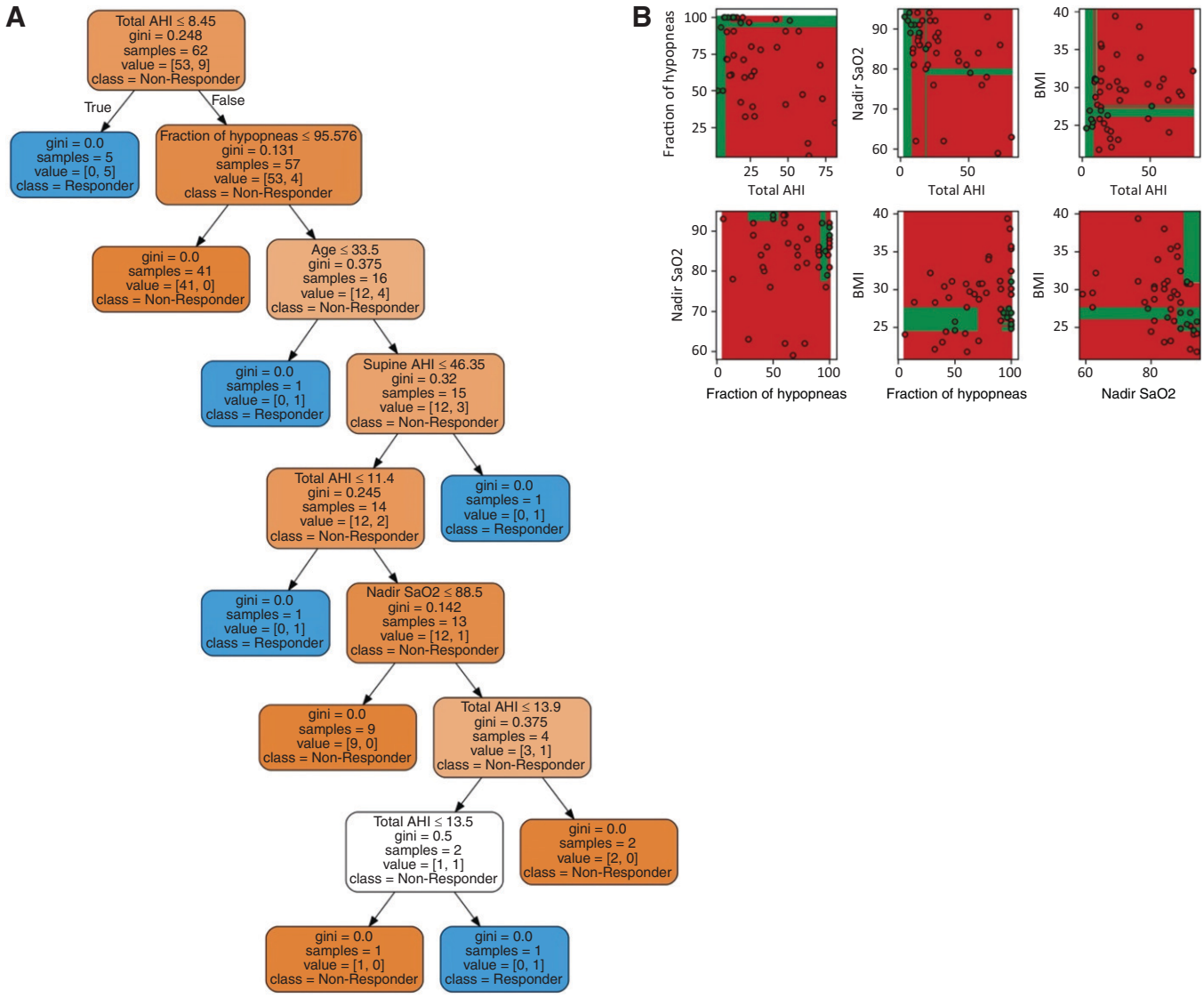
Participant characteristics

Baseline anthropometric and polysomnography characteristics for the study participants are displayed in Table 1. Overall, oral appliance therapy reduced (median and interquartile range) the total AHI by 46% (8%–67%).

Unsupervised separability assessment

Unsupervised clustering based on principal component analyses was used to estimate the linear separability of the input data into a 2-class-based classification system. Principal component analyses explained 88% of the information variance in the input data using the first 3 principal components. This result indicates that the key

Figure 2—Decision tree learner visualization outputs and decision tree surface plots.



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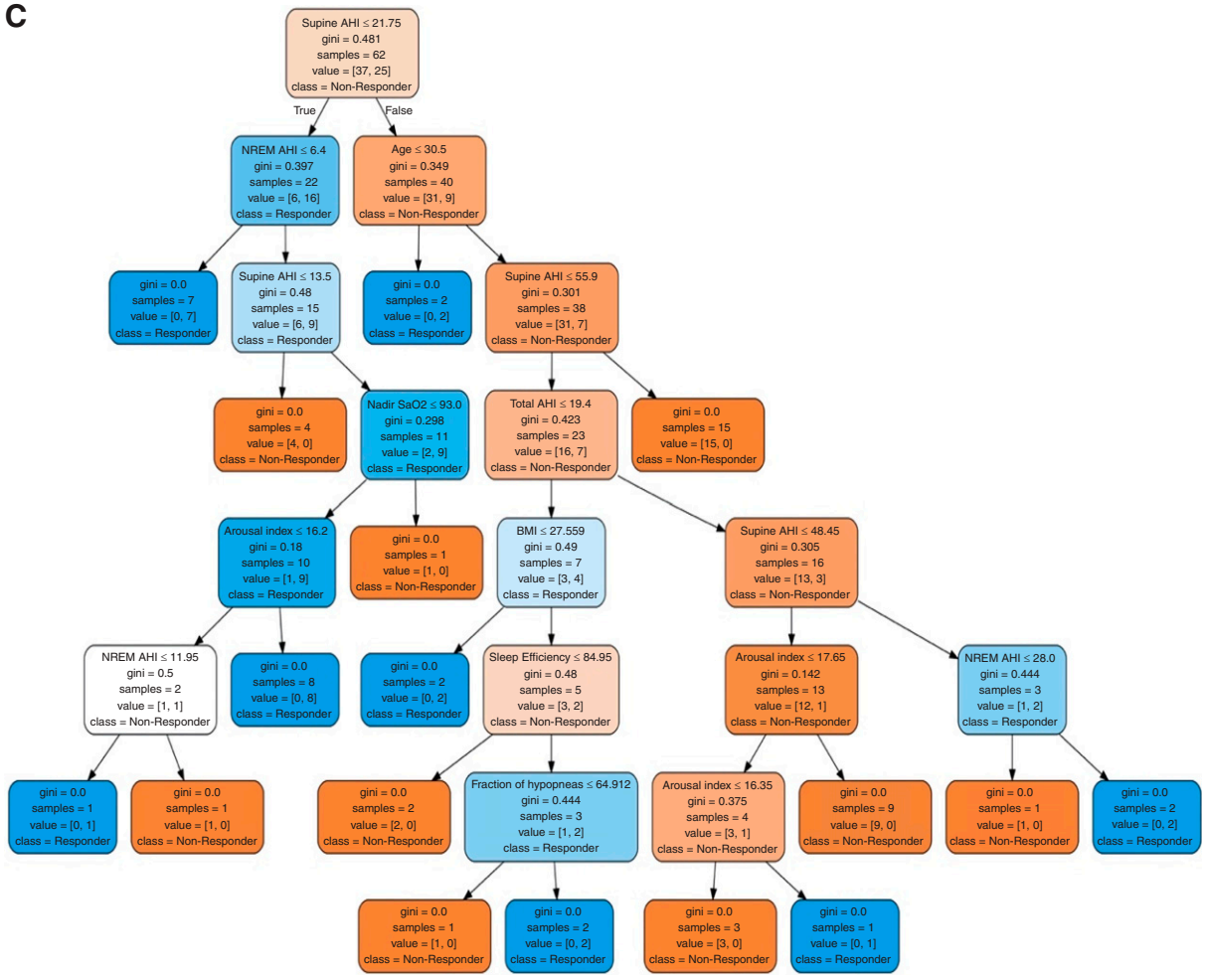
input variables contribute independently to classification and as such highlights the suitability to use the selected input variables for development of a supervised classifier to predict oral appliance therapy responders. The principal component analyses generate a projected score of the original data points defined by the values of the first 3 components. Plotting the projected 3-dimensional scores creates a comparative cluster plot (shown in **Figure 1** for each of the 4 treatment definitions assessed). The cluster plots showcase the physical separation between the responder and nonresponder classes represented by 2 separate clusters. This is a unique way to visualize the data space and separability between responder and nonresponder classes for each of the 4 treatment definitions. The principal component analyses results guided the next stage (step 2) of the machine-learning modeling with confidence, where supervised classifiers were employed.

Supervised training and model selection

Each of the 12 different supervised machine-learning classifiers provided high mean accuracy rates in the 10-fold validation assessments performed on the n = 45 training set. For example, for treatment definition 1 (AHI < 5 events/h), the lowest accuracy performance was acquired from the support vector machine classifier at 73% ± 15%, while the highest performance accuracy was acquired from the random forest classifier at 91% ± 8%. For treatment definition 2 (AHI < 10 events/h), the naïve Bayes classifier provided the highest accuracy at 73 ± 14%, and for definitions 3 (≥ 50% reduction in baseline AHI) and 4 (≥ 50% reduction in baseline AHI to < 20 events/h) the logistic regression classifier provided the highest performance accuracies at 66% ± 16% and 69% ± 11%, respectively. The best-performing models for each of the 4 treatment definitions were used in the independent validation testing (outlined below).

Figure 2—Decision tree learner visualization outputs and decision tree surface plots. (*Continued*)



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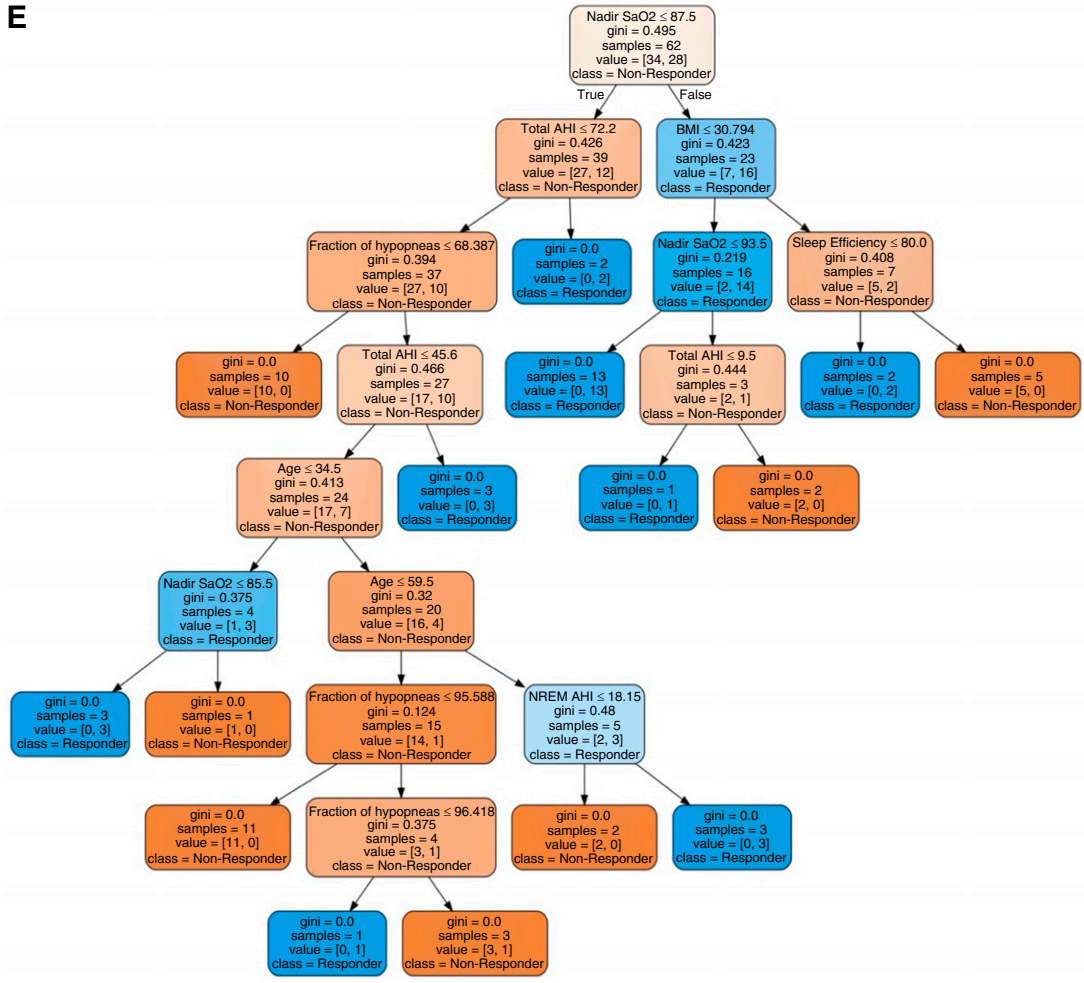
Independent validation

The independent validation accuracy results for each of the 4 treatment definitions and the accompanying individual responder prediction estimates for the 17 participants in the independent validation data set are provided in **Table 2**. Individual baseline and oral appliance treatment AHI values are also displayed in **Table 2**.

Visualization of the decision tree learner modeling

Decision tree learner outputs for the data for all 62 participants for each of the 4 treatment definitions are provided in **Figure 2**. Accompanying classification plots are also displayed to highlight the formation of classification boundaries for key input variable pairs.

Figure 2—Decision tree learner visualization outputs and decision tree surface plots. (*Continued*)



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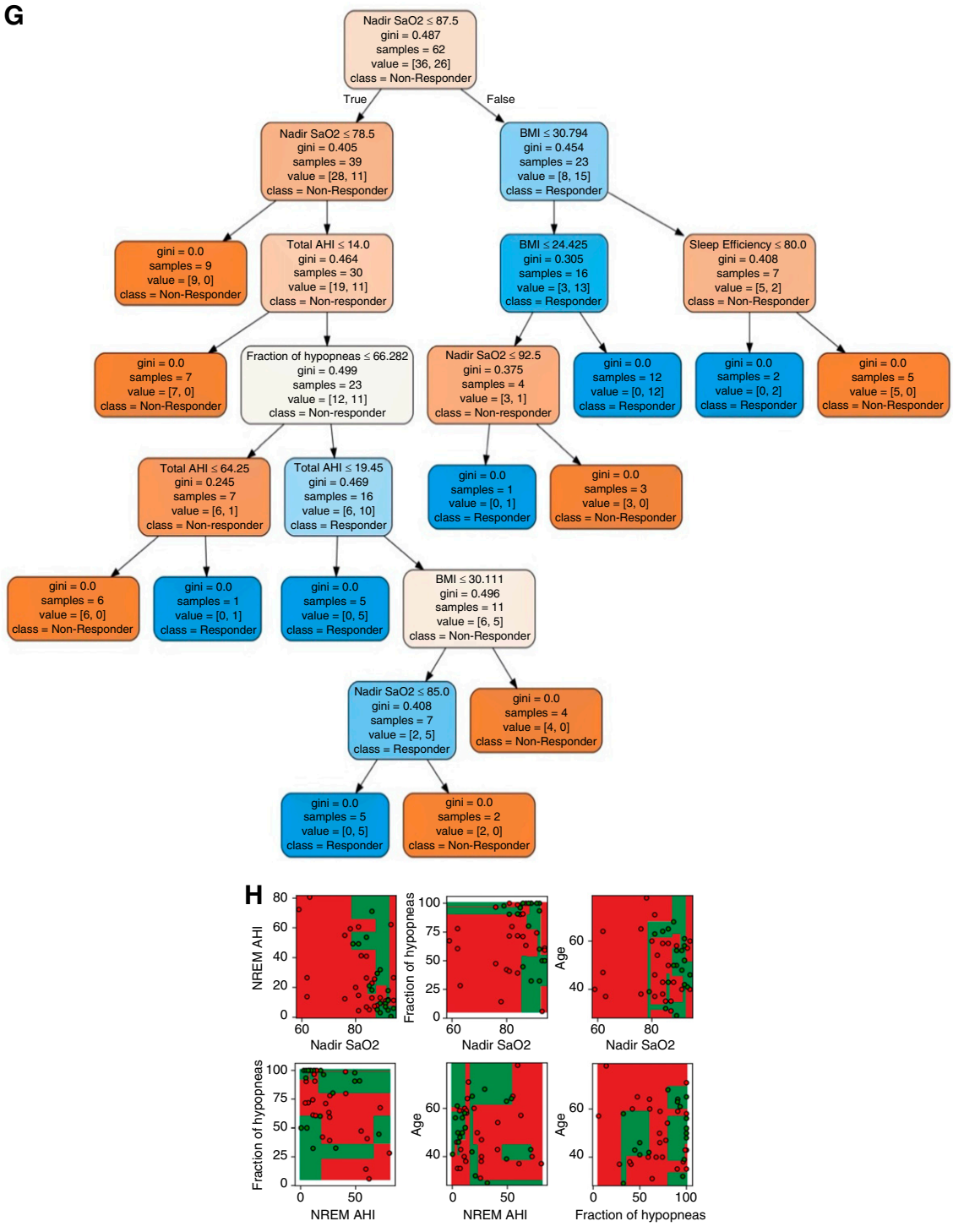
DISCUSSION

The main findings of this study are that a machine learning–based model underpinned by OSA endotype concepts that includes routinely collected sleep study and clinical data inputs may help predict treatment outcomes to oral appliance therapy for people with OSA. In addition, unlike most machine-learning approaches in which the underlying decisions of the model are not transparent, the complementary decision tree learner approach used in the current study allows for

Figure 2—Decision tree learner visualization outputs and decision tree surface plots. (*Continued*)



(A), **(C)**, **(E)**, and **(G)** provide structural views of the trained model and **(B)**, **(D)**, **(F),** and **(H)** show the decision tree surface plots for the key paired input variables that were used to derive the classification boundaries (where green indicates "responder" and red indicates "nonresponder") for each of the 4 treatment outcome definitions (**A** and **B** = AHI < 5 events/h, **C** and **D** = < 10 events/h, **E** and **F** = 50% reduction in the AHI, and **G** and **H** = 50% reduction in the AHI to < 20 events/h). The visualization outputs show the key input variables and the various threshold-based classification pathways for all of the 62 patients. "Gini" is a measure of how often a randomly chosen element from the data set is correctly labeled such that when it reaches its minimum (0) this indicates the end of a decision branch (ie, a selection is made where blue boxes indicate "responder" whereas dark orange boxes indicate "nonresponder"). "Samples" indicate the number of participants in each decision branch and "values" indicate the numbers estimated to be a "nonresponder" (left) or a "responder" (right). Arrows and boxes to the left indicate that the highlighted criterion is met (true) and boxes to right indicate that the criterion is not met (false). AHI = apnea-hypopnea index, BMI = body mass index, NREM = nonrapid eye movement, SaO_2 = oxygen saturation.

Table 1—Baseline anthropometric and polysomnography characteristics of the study participants (n = 62 participants [11 female]).

Age, y	49 ± 12
Body mass index, kg/m^2	28 ± 4
Apnea-hypopnea index (number of events/h)	26 ± 19
Nadir overnight oxygen saturation, %	84 ± 8
Arousal index (number of arousals/h)	24 ± 12
Rapid eye movement sleep apnea-hypopnea index (number of events/h)	30 ± 19
Supine apnea-hypopnea index (number of events/h)	36 ± 23
Nonrapid eye movement sleep apnea-hypopnea index (number of events/h)	24 ± 20
Fraction of hypopneas:apneas, %	75 ± 25

visualization of the data and model decisions to provide unique physiological insight and the opportunity for clinical oversight. While further validation in larger clinical data sets is required, this novel approach has the potential to be a useful clinical tool to help identify patients for oral appliance therapy to increase treatment success rates.

The patient journey for those prescribed oral appliance therapy is often time-consuming and costly.[9,10] For example, many have previously tried and failed CPAP therapy. Thus, by the time the patient receives an appropriately fitted and titrated oral appliance device they may have undergone multiple sleep studies and medical appointments (ie, sleep physician and dental visits). Accordingly, given the time and financial burden, understandably there is a strong desire and often an expectation for treatment success. Yet on average, roughly half of all patients prescribed oral appliance therapy currently have an incomplete therapeutic response.[8] This leaves many patients

Table 2—Prediction accuracy and responder classification probability results from the independent validation testing for each of the 4 treatment definitions.

			Definition 1	Definition 2	Definition 3	Definition 4
			(AHI < 5 events/h)	(AHI < 10 events/h)	(50% AHI reduction)	(50% AHI reduction to < 20 events/h)
Participant	Pre-AHI	Post-AHI	Responder Probability	Responder Probability	Responder Probability	Responder Probability
1	19	5.6	0.09	**0.40**	**0.05**	**0**
2	38.5	13.2	0.04	0.27	0.77	0.70
3	13.8	12.6	0.19	0.29	0.14	0
4	9.3	10.1	0.33	**0.55**	0	0
5	55.5	39	0.07	0.09	0	0
6	14.9	7.5	0.14	0.55	0.01	0.04
7	21	17.2	0.05	0.21	**0.82**	0
8	17	11.7	0.10	0.22	0	0
9	26.8	18.2	0	0.19	**0.83**	0
10	21.9	17	0.19	0.27	0.01	0
11	18.9	6.6	0.14	**0.28**	**0.01**	**0**
12	38	34.3	0.17	0.44	0	0
13	14.5	6.6	0.06	**0.30**	**0.32**	**0**
14	13.4	16	0.41	**0.63**	0	0.03
15	31.2	5.3	0.24	**0.30**	0.93	0.95
16	25.3	5.1	0.18	**0.41**	0.93	0.97
17	16.4	5.2	0.32	0.62	1	1
Prediction accuracy			17/17 (100%)	10/17 (59%)	12/17 (71%)	14/17 (82%)

Corresponding apnea-hypopnea index (AHI) values at baseline (pre-AHI) and on oral appliance therapy (post-AHI) are also displayed for each of the 17 participants. Responder probability indicates the estimated level of confidence of the model to predict that an individual was a responder to oral appliance therapy according to each of the 4 treatment outcome definitions. Values close to 1 indicate that the model had high confidence that the individual was a responder. Conversely, values close to 0 indicate that the model was very confident that the individual was a nonresponder to oral appliance therapy. Bold values indicate incorrect classification. For example, the AHI values indicate that participant 4 was a nonresponder according to all 4 treatment outcome definitions. The model correctly classified this in three-fourths of the treatment outcome definitions. However, in definition 2, where the treatment definition criterion was almost met (AHI = 10.1 events/h), the model had relatively low confidence of its prediction at only 55%. AHI – apnea-hypopnea index.

frustrated and disgruntled and at risk of not pursuing further treatment options to alleviate their OSA symptoms.

As such, development of clinically deployable tools to help predict who will respond to oral appliance therapy is a priority and has been the focus of considerable research effort. Clinical, demographic, and anthropometric characteristics such as lower body mass index, female sex, younger age, craniofacial characteristics, and smaller neck circumference have each been associated with favorable oral appliance treatment outcomes as has lower OSA severity as measured via the AHI.[8,28] However, in isolation, these measures often perform poorly as treatment predictors for oral appliance therapy.[29] Thus, detailed upper-airway imaging and OSA endotyping approaches have recently been investigated to provide more comprehensive insight into the physiological mechanisms and determinants of oral appliance treatment success with considerable predictive potential.[19–21,30,31] The current findings, which build upon an OSA endotype framework using standard clinical and polysomnographic inputs,[14] provide a potential pathway toward a more holistic physiology-based approach to oral appliance treatment prediction. As the inputs for this approach are readily available from a standard sleep study report/clinical assessment, this has considerable clinical translation potential.

Nonetheless, while the current findings are encouraging with prediction accuracy for each of the treatment outcome definitions beyond the current 50% success rate in the independent validation, with an increased volume of data, there is scope for iterative enhancement of the model to further improve treatment prediction accuracy. This requires further investigation, as does the need to determine the influence of different scoring criteria. Similarly, investigation into the prediction accuracy of the model for other oral appliances beyond the novel device studied here as well as other non-CPAP therapies is required. The 9 input variables used in the current study were selected based on prior studies that indicated their predictive potential when used in isolation and physiological rationale.[14] However, inclusion of additional input variables may also further enhance model performance. Of note, as highlighted in **Table 2**, when the model made an incorrect classification in many cases responder probability was close to 0.5. This indicates less classification certainty vs instances closer to 0 (highly unlikely to be a responder) or 1 (highly likely to be a responder). Thus, theoretically, in instances where model values are close to 0.5 this may trigger additional evaluation and/or clinical workup/predictive tools to inform treatment decisions to further improve overall treatment success rates.

In addition, there is scope to consider the results of all 4 treatment definitions collectively in combination with responder probability values and the decision tree learner outputs to inform clinical decision-making. Indeed, while reviewing the model prediction of a single treatment definition is helpful to compare with the literature across treatment modalities and to provide insight into specific outcomes of importance, evaluation of certain definitions in isolation may be of less value clinically. For example, in the current study many participants had baseline AHI values close to or below 20 events/h. Thus, assessment of the commonly used surgical definition of treatment success (50% reduction in AHI to < 20 events/h, definition 4) is less relevant in this context. However, consideration of summed model prediction data across all 4 treatment definitions, along with other clinical metrics/insight, could be invaluable to inform clinical decision-making ideally via a joint decision-making process between the clinician and patient (according to patient preferences/expectations). This approach may be particularly helpful for potential "borderline" cases. For example, examination of the data in **Table 2** indicates that the model correctly predicted that participants 1, 15, 16, and 17 were nonresponders according to definition 1 (AHI < 5 events/h). However, all these cases had major reductions in OSA severity with oral appliance therapy and were close to reaching the strict < 5 events/h treatment outcome definition. Thus, in practical terms, reductions in AHI of this magnitude to ∼5 events/h would typically be considered a clinical success. Consideration of the collective model output data could have helped identify high likelihood of a positive treatment outcome in at least 3 of these borderline cases (participants 15–17).

The decision tree visualization in **Figure 2** outlines the various ways in which the key clinical and polysomnography inputs can interact to guide the oral appliance treatment success/failure decisions of the model for the current data set. Influential contributors include those that have been identified in isolation as being important for oral appliance treatment outcome in prior studies such as AHI measures, age, and body habitus[8] as well as those that may be physiological surrogates of upper-airway collapsibility such as the fraction of hypopneas:apneas[32] and nadir overnight oxygen saturation.[33] Thus, these outputs could conceivably be automatically generated on an individual case basis as part of a standard sleep study report to highlight the decision processes of the model to provide additional clinical and physiological oversight.

In conclusion, these novel findings build on an increasing body of work aimed at developing practical physiological-based tools to better inform and direct treatment options for OSA including non-CPAP therapies tailored to individual underlying pathophysiology. Further model refinement in larger data sets to enhance prediction accuracy and prospective clinical studies is now required to determine the potential benefit that these tools may provide in practice.

ABBREVIATIONS

AHI, apnea-hypopnea index
CPAP, continuous positive airway pressure
OSA, obstructive sleep apnea

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