A Novel Model to Estimate Key Obstructive Sleep Apnea Endotypes from Standard Polysomnography and Clinical Data and Their Contribution to Obstructive Sleep Apnea Severity

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Abstract

Rationale: There are at least four key pathophysiological endotypes that contribute to obstructive sleep apnea (OSA) pathophysiology. These include *1*) upper-airway collapsibility (Pcrit); *2*) arousal threshold; *3*) loop gain; and *4*) pharyngeal muscle responsiveness. However, an easily interpretable model to examine the different ways and the extent to which these OSA endotypes contribute to conventional polysomnography-defined OSA severity (i.e., the apnea–hypopnea index) has not been investigated. In addition, clinically deployable approaches to estimate OSA endotypes to advance knowledge on OSA pathogenesis and targeted therapy at scale are not currently available.

Objectives: Develop an interpretable data-driven model to *1*) determine the different ways and the extent to which the four key OSA endotypes contribute to polysomnography-defined OSA severity and *2*) gain insight into how standard polysomnographic and clinical variables contribute to OSA endotypes and whether they can be used to predict OSA endotypes.

Methods: Age, body mass index, and eight polysomnography parameters from a standard diagnostic study were collected. OSA endotypes were also quantified in 52 participants (43 participants with OSA and nine control subjects) using gold-standard physiologic methodology on a separate night. Unsupervised multivariate principal component analyses and data-driven supervised machine learning (decision tree learner) were used to develop a predictive algorithm to address the study objectives.

Results: Maximum predictive performance accuracy of the trained model to identify standard polysomnography-defined OSA severity levels (no OSA, mild to moderate, or severe) using the using the four OSA endotypes was approximately twice that of chance. Similarly, performance accuracy to predict OSA endotype categories ("good," "moderate," or "bad") from standard polysomnographic and clinical variables was approximately twice that of chance for Pcrit and slightly lower for arousal threshold.

Conclusions: This novel approach provides new insights into the different ways in which OSA endotypes can contribute to polysomnography-defined OSA severity. Although further validation work is required, these findings also highlight the potential for routine sleep study and clinical data to estimate at least two of the key OSA endotypes using data-driven predictive analysis methodology as part of a clinical decision support system to inform scalable research studies to advance OSA pathophysiology and targeted therapy for OSA.

Keywords: upper airway; sleep-disordered breathing; precision medicine; lung; phenotyping

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Obstructive sleep apnea (OSA) is a common breathing disorder characterized by repetitive pharyngeal collapse during sleep (1). Untreated OSA is associated with many adverse health outcomes, including cardiovascular (2), metabolic (3), and neurocognitive consequences (4). Continuous positive airway pressure (CPAP), which acts as a pneumatic splint for the pharyngeal airway, is highly efficacious in resolving respiratory events in OSA. However, tolerance and adherence remain major limitations for CPAP therapy for many patients, with failure rates of 50% or more (5–7). Second-line therapies, such as oral appliances, tend to have higher adherence than CPAP (8). However, treatment efficacy varies and is currently very difficult to predict (9).

Anatomical and nonanatomical factors contribute to OSA pathogenesis (10, 11). Nonanatomical factors or "pathophysiological endotypes" (or "phenotypes," as they have previously been called) (10, 11), such as a low respiratory arousal threshold, oversensitive respiratory control system (high loop gain), and impaired upper-airway dilator muscle responsiveness during sleep are present in most people with OSA (11). In addition, some degree of anatomical impairment (i.e., narrow, crowded, collapsible airway) is a key feature of OSA for all patients (12–14). These four endotypes have been proposed to be important contributors to OSA pathogenesis and have provided new opportunities for targeted therapy (10, 11). However, the extent to which they contribute to standard polysomnography (PSG)-defined OSA severity categories (i.e., mild, moderate, and severe defined via the apnea–hypopnea index [AHI]) has not been systematically investigated.

Novel approaches to manipulate specific OSA endotypes to reduce OSA severity have been performed in small physiology studies (15–21). These studies provide proof-of-concept support for a targeted endotype-based model to treat OSA (22–26). However, the detailed physiological methodology used to accurately quantity OSA endotypes is invasive, time-consuming, and impractical for routine clinical care. Accordingly, a major objective to advance targeted therapy for OSA is to develop simplified techniques to accurately estimate the key endotypic traits. There has been recent progress toward achieving this goal. Indeed, simple approaches to estimate airway collapsibility using standard polysomnography and CPAP titration data (27–29) have been developed. Wakefulness tests have also been developed to estimate upper-airway collapsibility (Pcrit) during sleep (30, 31). In complementary work, tools to simply quantify the nonanatomical traits that contribute to OSA, such as loop gain (32–34), the respiratory arousal threshold (35, 36), and pharyngeal muscle effectiveness (29), have also been developed. However, many of these approaches estimate OSA endotypes by constraining the data to fit a specific model (i.e., a gain, delay, and single time-constant model) that may or may not represent the underlying dynamics in some patients. In addition, these approaches are yet to be translated to routine clinical care. Thus, there remains an important need to test additional tools to estimate OSA endotypes to inform targeted therapy that can be readily integrated into clinical care.

Accordingly, this study aimed to develop an interpretable data-driven model to determine *1*) the different ways and extent to which the four OSA pathophysiological endotypes contribute to polysomnographic measures of OSA severity; and *2*) gain insight into how standard polysomnographic and clinical variables contribute to OSA endotypes and whether standard polysomnographic and clinical variables can be used to predict key OSA endotypes.

Methods

Endotype data for the current study were acquired during a larger study to quantify the key pathophysiological traits causing OSA (11). The methodological details below focus on elements pivotal for the current novel investigations and only briefly outline the general experimental methodology described previously (10, 11). Data were collected in Boston and analyzed in Australia (Commonwealth Scientific and Industrial Research Organisation and Neuroscience Research Australia).

Participants

Complete data were acquired from 52 otherwise healthy individuals who were not receiving any medications known to affect sleep or breathing. Forty-three participants had OSA (total AHI >10 events/h sleep), and nine did not (total AHI <10 events/h sleep). Participants with OSA had been compliant (>4 h/night) with CPAP therapy assessed via machine download for at least 3 months before enrollment. Twenty-three participants from the original cohort of 75 who completed all the study procedures (11) were excluded, as they did not meet the criteria for one or more of the current analyses (i.e., incomplete data for one or more of the study parameters; *see* DATA ANALYSIS for further detail). All participants provided informed written consent. The protocol was approved by the Partners HealthCare Institutional Review Board.

Key Measurements

Protocol. Initially, a standard baseline in-laboratory PSG off CPAP was performed in all participants to quantify key PSG-measured variables of OSA severity. CPAP was withheld only during the night of the baseline PSG. Sleep studies were staged and respiratory events were scored by an experienced sleep technician blinded to the study objectives using standard criteria (37). Hypopneas were scored when there was either a >50% airflow reduction or a lesser airflow reduction–associated with a >3% oxygen desaturation or a cortical arousal (37). On a separate night, participants completed a detailed overnight physiology study. Electroencephalograms (C3-A2/O2-A1), electrooculograms, and chin electromyogram were acquired for sleep stage and arousal scoring. Genioglossus electromyogram was measured using fine-wire intramuscular electrodes (Cooner Wire Co.) (11, 38). Epiglottic pressure was acquired using a transducer-tipped pressure catheter (Millar Instruments) (11). A nasal CPAP mask was fitted, and pressure/airflow was measured with pressure transducers (Validyne Corporation) and pneumotachograph (Hans Rudolf Inc) (11).

Participants were studied supine on CPAP at a level to eliminate inspiratory flow limitation. Transient reductions in CPAP of varying magnitude were applied for ⩽3 minutes during stable non–rapid eye movement (NREM) sleep to cause varying degrees of upper-airway collapse to quantify the four OSA endotypes, as described in detail elsewhere (10, 11, 39).

Data and statistical analyses approaches. Outcomes were categorized to facilitate predictive quantitative analyses. Accordingly, to address how and whether OSA endotypes contribute to PSG-defined

OSA severity, OSA severity categories were defined *a priori* as follows: *1*) no OSA (AHI <10 events/h sleep), mild to moderately severe OSA (AHI between 10 events/h sleep and 30 events/h sleep) and severe OSA (AHI >30 events/h sleep) for each AHI parameter examined (total AHI, NREM AHI, and rapid eye movement [REM] AHI). Similarly, to develop predictive analysis methodology to gain insight into the different ways polysomnographic and clinical variables can contribute to OSA endotypes and whether they can be used for prediction purposes, each OSA endotype was categorized as "good," "moderate," or "bad" according to previously defined physiological cutoffs (10, 11) (Table 1). Age, body mass index (BMI), and the eight standard polysomnography measures from the manually scored PSG (including total AHI, supine AHI, nadir arterial oxygen saturation, NREM AHI, supine NREM AHI, REM AHI, arousal index, and the fraction of hypopneas vs. apneas) were used for predication outcome analyses. These variables were selected because they have, in isolation, been shown to be related to one or more of the OSA endotypes in previous studies (40–51). To be included in the analyses, participants from the parent study (11) had to have complete data for all four endotypic traits from the physiology night plus measures for age, BMI, and the eight standard PSG variables mentioned above.

A detailed description of the methodological background and the data and statistical analysis approaches performed in this study is outlined in the online supplement. Briefly, developing an easily interpretable predictive algorithm with the potential to learn OSA severity categories from OSA endotype data and the use of clinical data and standard PSG variables to predict OSA endotypes requires an ensemble of novel algorithms. Accordingly, unsupervised data analysis techniques coupled with supervised predictive modeling were chosen as a state-of-the-art methodology to support clinical evaluation and satisfy the decision-making objectives of this study.

Specifically, we used unsupervised multivariate principal component analyses (PCAs) and data-driven supervised machine learning using a decision tree learner (DTL). Unlike other machine learning techniques, which resemble a "black box" approach in which the underlying computational decisions are unknown to the user, the current approach has the advantage of a visualization output of the clinical decision tree that can be reviewed by the user. This provides novel insight into the different ways by which OSA endotypes can contribute to OSA severity and how standard polysomnographic and clinical data can contribute to OSA endotypes in the current cohort. Each treatment decision tree was trained and then tested using a leave-one-out cross-validation approach. This was repeated 52 times to assess the accuracy of the model for each outcome measure and was reported as accuracy versus DTL complexity plotted across the complexity parameter α. The α value determines the complexity of the tree by controlling the number of leaf nodes, with $\alpha = 0$ corresponding to the most complex tree and higher α values reducing the tree complexity and, hence, the tendency to overfit to the training data. Maximal performance accuracy during testing of the trained and optimized (balanced for accuracy and complexity) DTLs are reported in the text. Preprocessing and analyses were conducted in house with customized software developed at Commonwealth Scientific and Industrial Research Organisation, Australia. Sensitivity analyses were also conducted using multinomial logistic regression to model OSA severity categories and obtain accuracy estimates.

Results

Anthropometric sleep characteristics and objective CPAP compliance of the 52 study participants with complete data are summarized in Table 2. On average, study participants had 39 ± 25 minutes of REM sleep and spent 302 ± 74 minutes supine during their diagnostic study. Reasons for data loss/exclusion for 23 of the 75 participants from the original cohort include inability to quantify one ($n = 20$) or two ($n = 2$) of the four traits. Another participant did not have any supine sleep on their baseline diagnostic study. Age, BMI, and total AHI characteristics for the 52 participants with complete data who were included in the current study were not different from the 23 participants with incomplete data from the larger cohort who were not included (Table E1).

PCA using the four OSA endotypes, clinical variables, and eight PSG variables showed linear separability with the first two components (Figures E1 and E2). Having confirmed linear separability (requirement to proceed with the subsequent analysis techniques/steps), we developed an algorithm to address the study objectives.

Detailed Physiological Measurements of the Four Key Endotypes to Classify OSA Severity Categories

The four OSA endotypes were used to train a supervised DTL model to gain insight into the different ways by which OSA endotypes can contribute to OSA severity and

Table 1. Three-class physiological threshold definitions for each OSA endotype

Class Definition	Pcrit (*cm H_2O*)	Loop Gain (*Dimensionless*)	Arousal Threshold (*cm H_2O*)	Muscle Responsiveness (*%Max EMG/−cm H_2O*)
Good	<−2	>−3	<−20	<−0.5
Moderate	−2 to +2	−3 to −5	−15 to −20	−0.1 to −0.5
Bad	>2	<−5	>−15	>−0.1

Definition of abbreviations: OSA = obstructive sleep apnea; Pcrit = upper-airway collapsibility; %Max EMG/−cm H_2O = genioglossus electromyography (EMG) as a percentage of maximal (Max) activation during wakefulness per cm H_2O of negative epiglottic pressure during sleep.
Definitions were defined according to previously established cutoffs (11). Good Pcrit = minimally collapsible upper airway, whereas bad Pcrit = highly collapsible upper airway. Good loop gain = low loop gain, whereas bad loop gain = high loop gain. Good arousal threshold = high arousal threshold (harder to wake up), whereas bad arousal threshold = low arousal threshold (easy to wake up). Good muscle responsiveness = excellent genioglossus muscle activation to small changes in negative pharyngeal pressure, whereas bad muscle responsiveness = poor genioglossus muscle responsiveness. In each case, moderate = intermediate values.

Table 2. Anthropometric and sleep parameters

	All Participants (*n* = 52)	Participants with OSA (*n* = 43)	Control Subjects (*n* = 9)
Sex, M/F	33/19	30/13	3/6
Age, yr	45 ± 11	47 ± 10	39 ± 13
BMI, kg/m^2	34 ± 7	35 ± 6	27 ± 4
Total AHI, events/h	36 ± 30	43 ± 29	4 ± 3
Supine proportion, %TST	89 (75, 93)	88 (73, 91)	95 (92, 98)
Supine AHI, events/h	37 ± 31	44 ± 29	4 ± 3
Nadir Sa_{O_2}, %	83 ± 7	82 ± 7	89 ± 3
NREM AHI, events/h	35 ± 32	42 ± 31	3 ± 4
Supine NREM AHI, events/h	37 ± 33	44 ± 32	3 ± 4
REM AHI, events/h sleep	37 ± 25	42 ± 24	13 ± 10
Arousal index, arousals/h sleep	37 ± 27	42 ± 27	14 ± 6
Fraction of hypopneas:apneas	86 ± 17	85 ± 19	90 ± 9
CPAP compliance, h/night	—	6.3 ± 1.4	—

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; F = female; M = male; NREM = non-REM; OSA = obstructive sleep apnea; REM = rapid eye movement; Sa_{O_2} = estimated overnight blood oxygen saturation; TST = total sleep time. Data are mean ± SD or median (25th centile, 75th centile).

determine whether they could be used to predict OSA severity category (no OSA, mild to moderately severe, or severe). Maximal performance accuracy of the optimized trained decision trees to predict the three OSA categories for each of the AHI definitions was approximately twice that of chance (total AHI = 56%, NREM AHI = 65%, and REM AHI = 64%). Full accuracy versus complexity plots and corresponding DTLs at or near maximal predictive accuracy are displayed in the online supplement (Figures E3 and E4). Figure 1 displays the output of the fully trained DTL (effective $\alpha = 0$) for the total AHI. The entire learning process within the decision tree predictor has been visualized to provide insight into the different ways by which OSA endotypes can contribute to OSA severity and face validity of the various pathways to correct prediction for the current cohort.

Multinomial logistic regression analyses also showed that the four key OSA endotypes could be used to estimate OSA severity category (Tables E2–E4). Accuracy performance characteristics for these analyses are displayed in Table E5.

Development of an Interpretable Model to Gain Insight into the Different Ways Standard Clinical and Polysomnographic Parameters Can Contribute to OSA Endotypes and Potential for These Variables to be Used to Predict OSA Endotypes

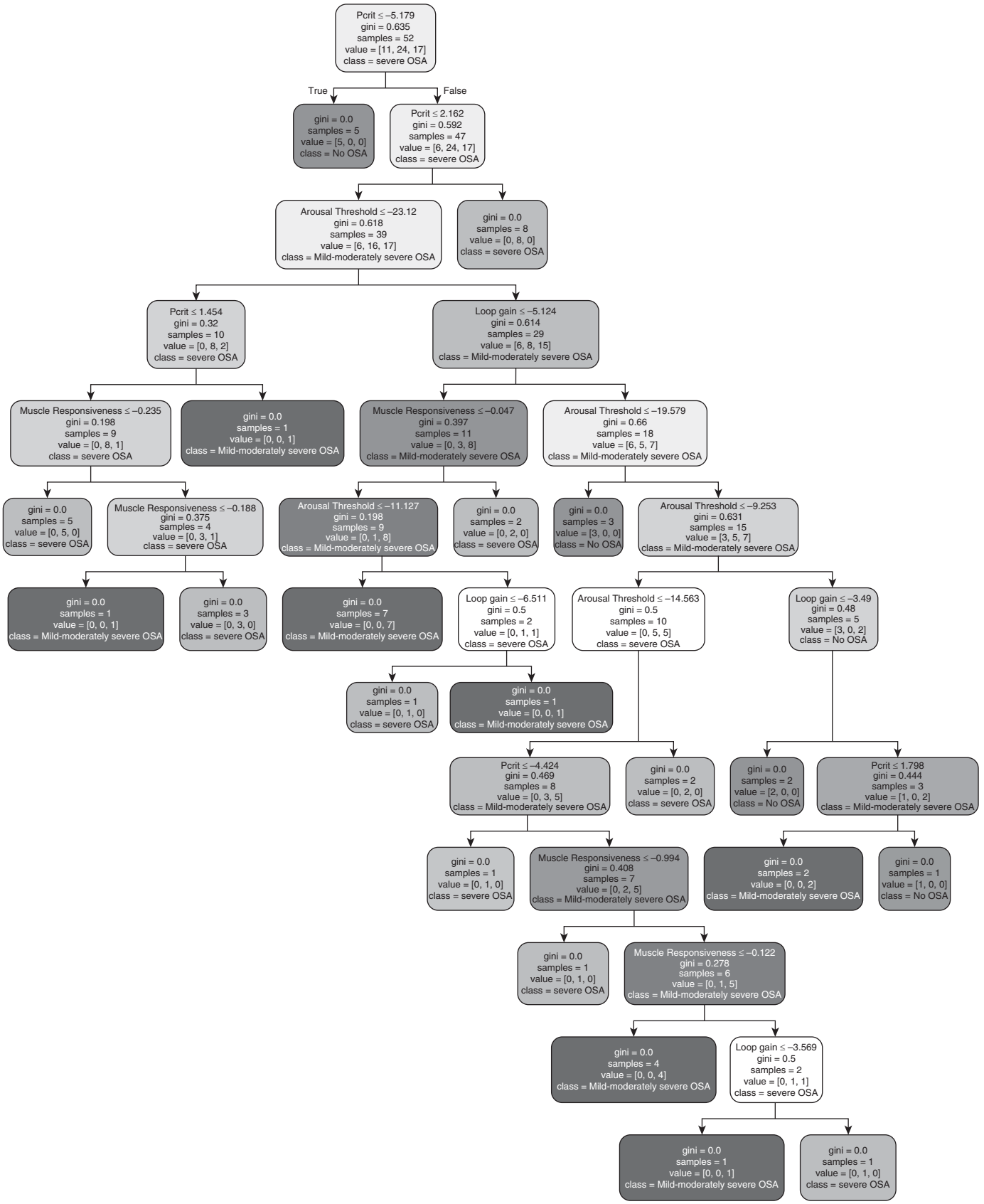
Age, BMI, and the eight selected PSG parameters were used to train a supervised DTL model to predict each OSA endotype. Maximal performance accuracy of the optimized trained decision trees to predict the three OSA endotype categories (good, moderate, and bad) was approximately twice that of chance for Pcrit (65%) and slightly lower for arousal threshold (56%). Conversely, maximum performance accuracy for loop gain and muscle responsiveness were similar to chance (40% and 41% respectively). Full accuracy versus complexity plots and corresponding DTLs at or near maximal predictive accuracy for Pcrit and arousal threshold are displayed in the online supplement (Figures E5 and E6). Figures 2A–2D display the complete outputs of the fully trained DTL (effective $\alpha = 0$) for Pcrit, arousal threshold, muscle responsiveness, and loop gain to provide insight into the different ways by which standard polysomnographic and clinical variables can contribute to OSA endotypes for the current cohort.

Discussion

The findings from this study provide support for the importance of OSA endotypes as key contributors to PSG-defined OSA severity. In addition, the study findings highlight the potential for routine clinical and PSG data to be used to estimate at least two of the key OSA endotypes using data-driven predictive analysis. Although further validation in larger prospective cohorts is required, the novel analytical approaches described in the current study have the potential to be incorporated as part of a clinical decision support system to inform targeted therapy for OSA.

Contribution of Endotypes to OSA Severity

Although this is the first study to use PCA and data-driven DTL approaches to investigate the contribution of all four OSA endotypes to OSA severity categories, several studies have explored potential relationships between individual OSA endotypes and OSA severity. For example, Pcrit correlates with OSA severity as measured via the AHI or respiratory disturbance index (40–42). However, the proportion of variance in AHI that Pcrit alone explains is quite low (*r* values range from 0.23 to 0.59) (40–42). Higher arousal threshold values correlate with increasing AHI and explain a substantial proportion of total AHI variance (*r* values range from 0.61 to 0.69) (35, 44). This may be, at least in part, due to greater sleep debt with increasing OSA severity (52). Earlier studies showed that higher loop gain values were associated with increased OSA severity as measured via the AHI (53). However, subsequent studies have shown that the influence of high loop gain on the AHI is dependent on Pcrit (11, 54). Few studies have explored potential relationships with pharyngeal muscle responsiveness and AHI. We did not find any independent relationship between muscle responsiveness and AHI in our original OSA endotyping/phenotyping cohort (50). Thus, previous studies have shown either no relationship or weak to moderate associations between individual OSA endotypes and OSA severity (50).


Pcrit ≤ −5.179
gini = 0.635
samples = 52
value = [11, 24, 17]
class = severe OSA
True
False
gini = 0.0
samples = 5
value = [5, 0, 0]
class = No OSA
Pcrit ≤ 2.162
gini = 0.592
samples = 47
value = [6, 24, 17]
class = severe OSA
Arousal Threshold ≤ −23.12
gini = 0.618
samples = 39
value = [6, 16, 17]
class = Mild-moderately severe OSA
gini = 0.0
samples = 8
value = [0, 8, 0]
class = severe OSA
Pcrit ≤ 1.454
gini = 0.32
samples = 10
value = [0, 8, 2]
class = severe OSA
Loop gain ≤ −5.124
gini = 0.614
samples = 29
value = [6, 8, 15]
class = Mild-moderately severe OSA
Muscle Responsiveness ≤ −0.235
gini = 0.198
samples = 9
value = [0, 8, 1]
class = severe OSA
gini = 0.0
samples = 1
value = [0, 0, 1]
class = Mild-moderately severe OSA
Muscle Responsiveness ≤ −0.047
gini = 0.397
samples = 11
value = [0, 3, 8]
class = Mild-moderately severe OSA
Arousal Threshold ≤ −19.579
gini = 0.66
samples = 18
value = [6, 5, 7]
class = Mild-moderately severe OSA
gini = 0.0
samples = 5
value = [0, 5, 0]
class = severe OSA
Muscle Responsiveness ≤ −0.188
gini = 0.375
samples = 4
value = [0, 3, 1]
class = severe OSA
Arousal Threshold ≤ −11.127
gini = 0.198
samples = 9
value = [0, 1, 8]
class = Mild-moderately severe OSA
gini = 0.0
samples = 2
value = [0, 2, 0]
class = severe OSA
gini = 0.0
samples = 3
value = [0, 0, 3]
class = No OSA
Arousal Threshold ≤ −9.253
gini = 0.631
samples = 15
value = [3, 5, 7]
class = Mild-moderately severe OSA
gini = 0.0
samples = 1
value = [0, 0, 1]
class = Mild-moderately severe OSA
gini = 0.0
samples = 3
value = [0, 3, 0]
class = severe OSA
gini = 0.0
samples = 7
value = [0, 0, 7]
class = Mild-moderately severe OSA
Loop gain ≤ −6.511
gini = 0.5
samples = 2
value = [0, 1, 1]
class = severe OSA
Arousal Threshold ≤ −14.563
gini = 0.5
samples = 10
value = [0, 5, 5]
class = severe OSA
Loop gain ≤ −3.49
gini = 0.48
samples = 5
value = [3, 0, 2]
class = No OSA
gini = 0.0
samples = 1
value = [0, 1, 0]
class = severe OSA
gini = 0.0
samples = 1
value = [0, 0, 1]
class = Mild-moderately severe OSA
Pcrit ≤ −4.424
gini = 0.469
samples = 8
value = [0, 3, 5]
class = Mild-moderately severe OSA
gini = 0.0
samples = 2
value = [0, 2, 0]
class = severe OSA
gini = 0.0
samples = 2
value = [2, 0, 0]
class = No OSA
Pcrit ≤ 1.798
gini = 0.444
samples = 3
value = [1, 0, 2]
class = Mild-moderately severe OSA
gini = 0.0
samples = 1
value = [0, 1, 0]
class = severe OSA
Muscle Responsiveness ≤ −0.994
gini = 0.408
samples = 7
value = [0, 2, 5]
class = Mild-moderately severe OSA
gini = 0.0
samples = 2
value = [0, 0, 2]
class = Mild-moderately severe OSA
gini = 0.0
samples = 1
value = [1, 0, 0]
class = No OSA
gini = 0.0
samples = 1
value = [0, 1, 0]
class = severe OSA
Muscle Responsiveness ≤ −0.122
gini = 0.278
samples = 6
value = [0, 1, 5]
class = Mild-moderately severe OSA
gini = 0.0
samples = 4
value = [0, 0, 4]
class = Mild-moderately severe OSA
Loop gain ≤ −3.569
gini = 0.5
samples = 2
value = [0, 1, 1]
class = severe OSA
gini = 0.0
samples = 1
value = [0, 0, 1]
class = Mild-moderately severe OSA
gini = 0.0
samples = 1
value = [0, 1, 0]
class = severe OSA

Conversely, although the current analyses approaches are not directly comparable with previous independent analyses, the present findings indicate that when all four OSA endotypes are considered collectively using a DTL approach, AHI-defined OSA severity categories can be distinguished. This is further supported by the multinomial logistic regression analyses findings. Thus, OSA endotypes appear to be important contributors to AHI-defined OSA severity categories.

In addition, the information provided in Figure 1 provides novel insight into the various ways in which people can either be protected from or have OSA depending on their endotypic traits. For example, consistent with the importance of upper-airway anatomy/collapsibility as an essential contributor to OSA pathogenesis (10, 11), at step 1 of the decision tree, if someone has a Pcrit $<\sim -5$ cm H_2O, they are protected from OSA ("no OSA" box on the upper left side of the decision tree in Figure 1). Conversely, if someone has a Pcrit $>\sim +2$ cm H_2O (severely collapsible airway), then this is a direct pathway to severe OSA ("severe OSA" box on the upper righthand side of the decision tree in Figure 1). However, as highlighted in Figure 1, if someone has a Pcrit $<\sim +2$ cm H_2O (mild to moderately collapsible airway), whether they have OSA (and if so, its severity) is dependent on the extent to which one or more of the other three nonanatomical traits are impaired. Thus, this decision tree approach provides unique insight into the various potential mechanisms that can contribute to OSA pathogenesis.

A Novel Simplified Approach to Estimate OSA Endotypes from Standard Clinical and PSG Variables

Recent advances in simplified measures for respiratory endophenotyping of OSA allow estimation of three of the four traits that contribute to an individual's OSA from a standard diagnostic sleep study or a CPAP titration (9). These include estimates of pharyngeal collapsibility (27, 28), arousal threshold (35, 36), and loop gain (34). These surrogate measures have been derived to translate complex respiratory endophenotyping methodology, which provides precise, detailed insight in a reproducible manner for research purposes (39, 55), to the clinical setting to allow tailored therapy for OSA (10). Simplified methods to estimate muscle responsiveness (the final trait) have proved more challenging. However, simply quantifying mean airflow during sleep may provide some insight into the combined contributions of upper-airway anatomy and pharyngeal muscle compensation (27, 28). In addition, a high REM AHI but low NREM AHI is likely to be a marker of excellent pharyngeal muscle effectiveness during NREM sleep (48). Thus, although the current study focused on gold-standard quantification of the muscle responsiveness endotype, investigation of muscle effectiveness or airflow responses/upper-airway gain would be of interest in future work.

Sands and colleagues have developed a composite approach in which all four endotypic traits are estimated by fitting a gain, delay, and time-constant model to the airflow signal from a standard PSG (26, 29, 36). This technique yields quite accurate estimates of each trait compared with more direct physiology assessments. A limitation of this approach is that it makes certain assumptions that may or may not be true in everyone. For example, it assumes that the airway is fully patent at the end of respiratory events such that ventilation matches ventilatory drive for several breaths before the resumption of sleep. This may not be true for everyone. Accordingly, this technique continues to be refined and optimized. Nonetheless, despite these potential limitations, using this approach in which information from all four OSA endotypic traits are considered can provide important insight into clinical responses to non-CPAP therapies. Indeed, it has recently been used to predict treatment response to oral appliances and oxygen therapy (21, 26). These findings further highlight the importance of incorporating all four traits into a prediction model to achieve predictive accuracy that is clinically useful.

The current study findings raise the possibility that a data-driven predictive analysis approach could be incorporated as part of a clinical decision support system to inform targeted therapy for OSA. We selected a total of eight standard PSG variables and two clinical variables to develop the predictive decision tree in the current study, as these are readily available and have, in isolation, been shown to be related to one or more of the OSA endotypes (40–51). Figure 2 highlights how each of these variables can contribute to the endotypic traits according to the stepwise decision tree developed by the model, which similar to Figure 1, provide novel mechanistic and clinical insight. Although the current approach yielded maximum estimates that are potentially clinically acceptable for Pcrit and arousal threshold, there is clearly further scope to add input from additional variables in future investigations to further optimize performance and predictive capacity. Similarly, like other recent attempts to estimate nonanatomical traits, accurate prediction for traits such as muscle responsiveness was suboptimal. Indeed, although these initial findings represent the first crucial analytical development step and provide novel mechanistic insight for the current cohort, further development and replication in other OSA endotype cohorts to determine whether the specific decision tree criteria derived here are generalizable to other cohorts is clearly required.

Methodological Considerations

Despite its novelty and strengths, this study has several limitations that need to be considered. First, the number of samples was quite low for a supervised model. However, the quality of the OSA endophenotypic data, which were collected using advanced physiological methodology, was very high. Thus, it was possible to achieve quite high maximal accuracy rates for OSA severity categories, Pcrit, and arousal threshold with a relatively small

Figure 1. (*Continued*). Decision tree for total apnea–hypopnea index (AHI) prediction using the four obstructive sleep apnea endotypes. This figure shows the internal workings of the algorithm. Gini impurity is a measure of how often a randomly chosen element from the set would be incorrectly labeled if it was randomly labeled according to the distribution of labels in the subset. It reaches its minimum (0) when all cases in the node fall into a single target category. At that stage, the "root nodes" converge into a "leaf node," demarking the end of a decision branch, or a root node itself becomes a leaf node with gini = 0. Left indicates that the criterion is met (true), whereas right indicates that the criterion is not met (false). Refer to the text and DISCUSSION explanation for further detail. Mild to moderately severe obstructive sleep apnea (OSA) = apnea–hypopnea index (AHI) between 10 and 30 events/h sleep; no OSA = AHI $<$ 10 events/h sleep; and severe OSA = AHI $>$ 30 events/h sleep. gini = gini impurity; Pcrit = upper-airway collapsibility; Sa_{O_2} = arterial oxygen saturation.

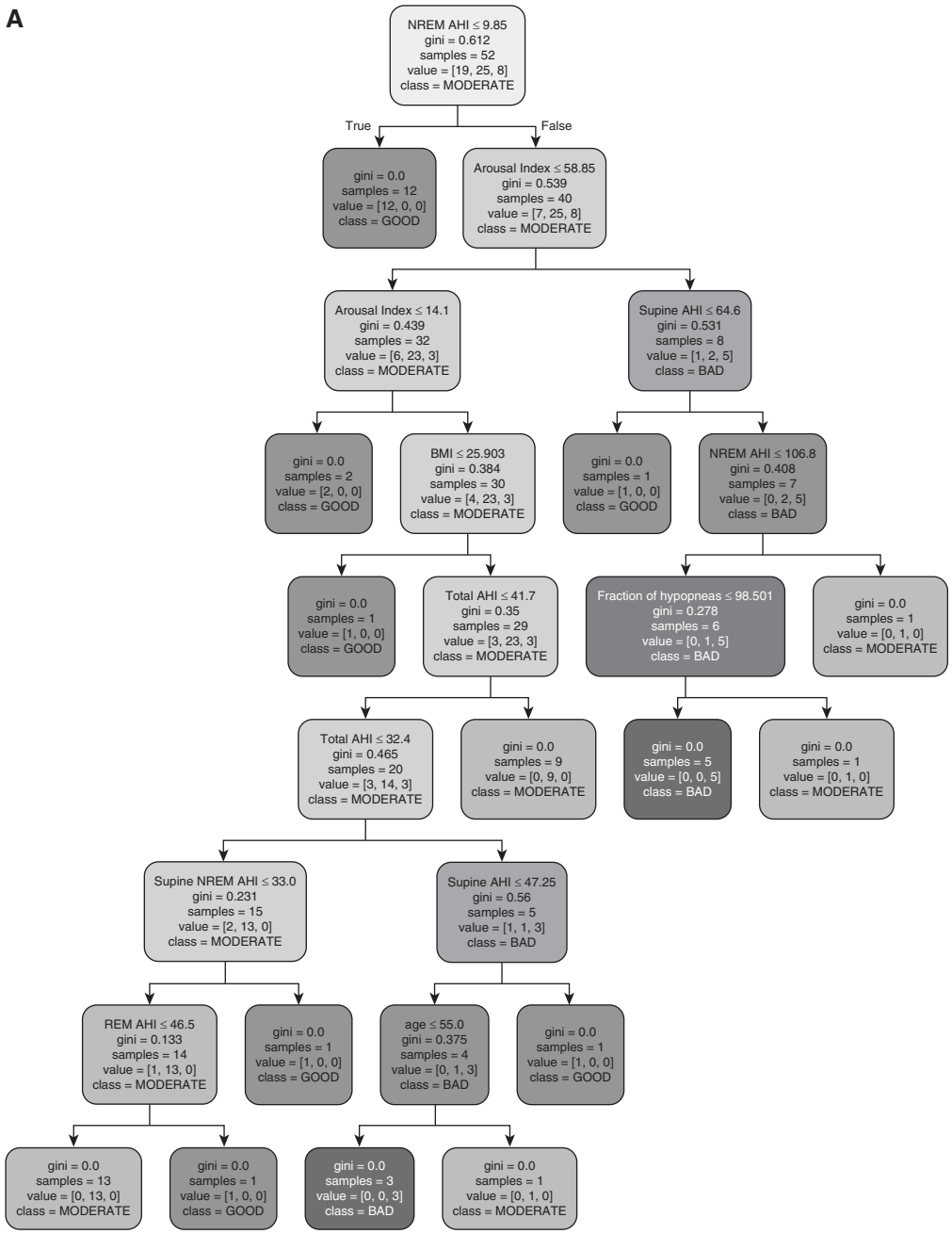


Figure 2. Decision tree predictions for the four obstructive sleep apnea endotypes using standard polysomnographic variables plus clinical data. (*A*) Upper-airway collapsibility. (*B*) Arousal threshold. (*C*) Muscle responsiveness. (*D*) Loop gain. AHI = apnea–hypopnea index; BMI = body mass index; gini = gini impurity; NREM = non–rapid eye movement; Pcrit = upper-airway collapsibility; REM = rapid eye movement; Sa_{O_2} = arterial oxygen saturation (*see* Table 1 for Good, Moderate, and Bad class definitions).

sample. Although the acquisition of larger detailed OSA endophenotyping datasets in which to compare/validate against the current findings would be desirable, this is impractical given the high level of complexity to acquire detailed endophenotypic data, including Pcrit and muscle responsiveness, using intramuscular electromyographic techniques. An alternate strategy would be to refine the tools described in the current study and apply to large OSA treatment datasets to assess predictive accuracy. Indeed, prediction accuracy could be further improved over time with more research on the suitability of various analysis models. This is a priority for future work but is beyond the scope of the current investigation.

There are several common definitions of hypopneas. Different definitions have the potential to alter AHI cutoffs (56) and polysomnography predictors of endotypic traits such as arousal threshold (57). Thus, as different hypopnea definitions have the potential to alter performance characteristics of the current algorithm that have been developed

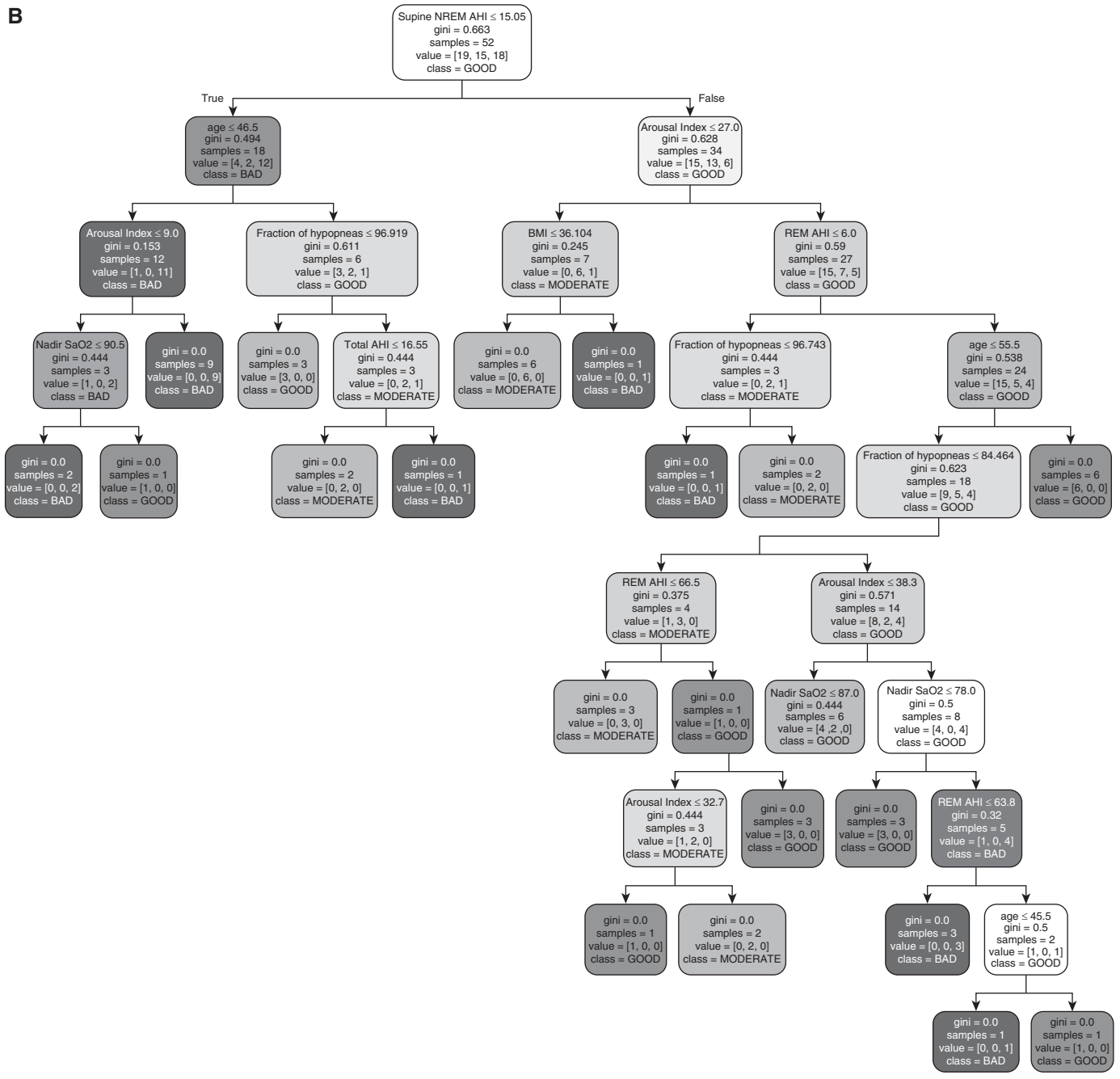


Figure 2. (*Continued*).

according to the selected clinical and physiological cutoffs, it will be important to develop and optimize future versions for different hypopnea/scoring criteria and different cutoffs as required. There is also considerable night-to-night variability in OSA severity as measured by the AHI and polysomnography parameters (58, 59). Thus, multiple night testing, potentially including home testing, to derive an average may help to reduce this source of variability and improve predictive accuracy performance. Study participants were CPAP compliant. OSA severity does not immediately to return to baseline levels after one night of CPAP withdrawal as employed in the current design (60–63). Thus, although of one night of withdrawal was appropriate to reduce the impact of potential confounders such as edema and sleep deprivation between study nights, it will be important to include the clinically relevant target group of untreated patients in future treatment prediction studies that use these analysis tools to enhance generalizability. Control subjects were also not matched to participants with OSA in

C

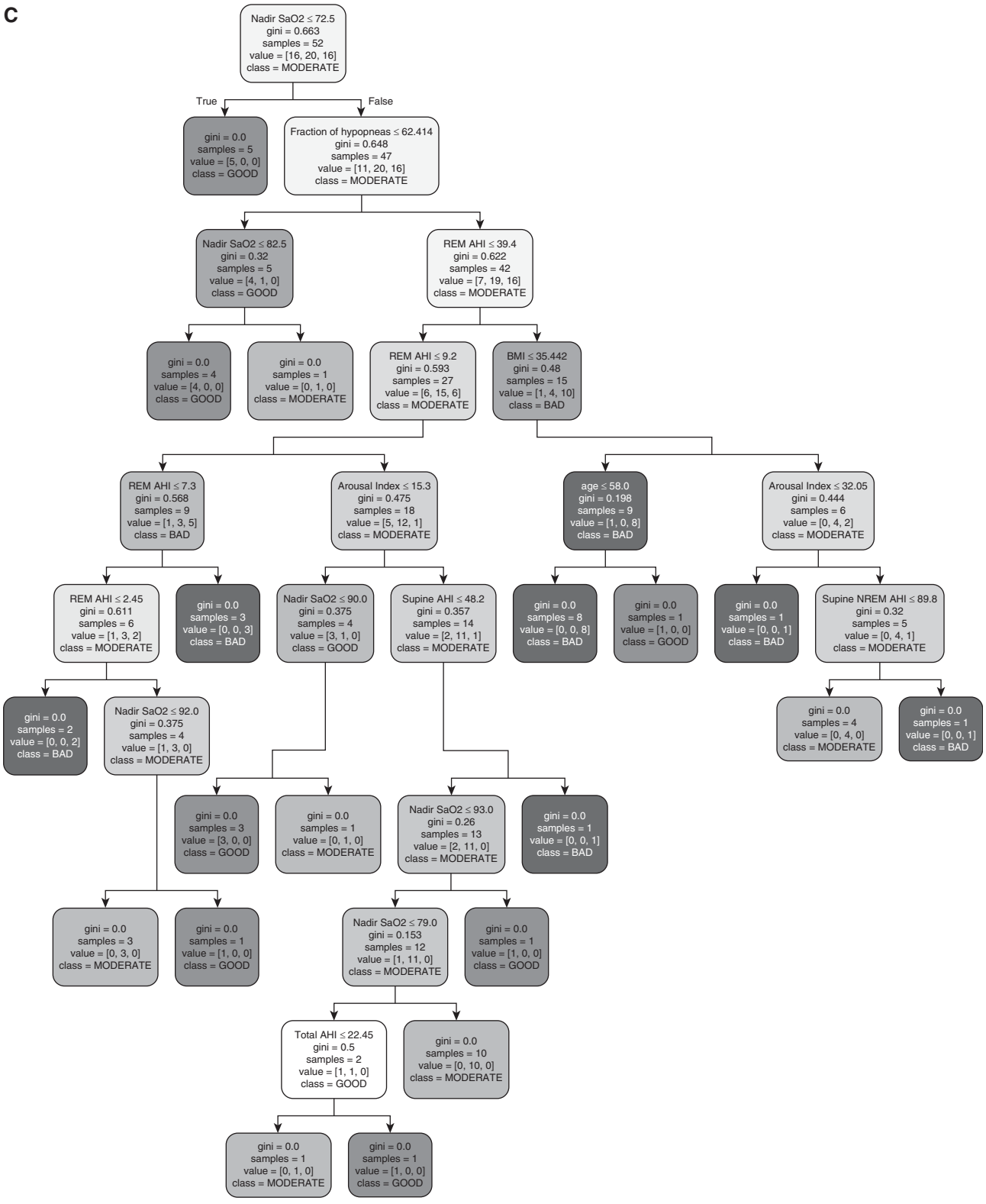


Figure 2. (*Continued*).

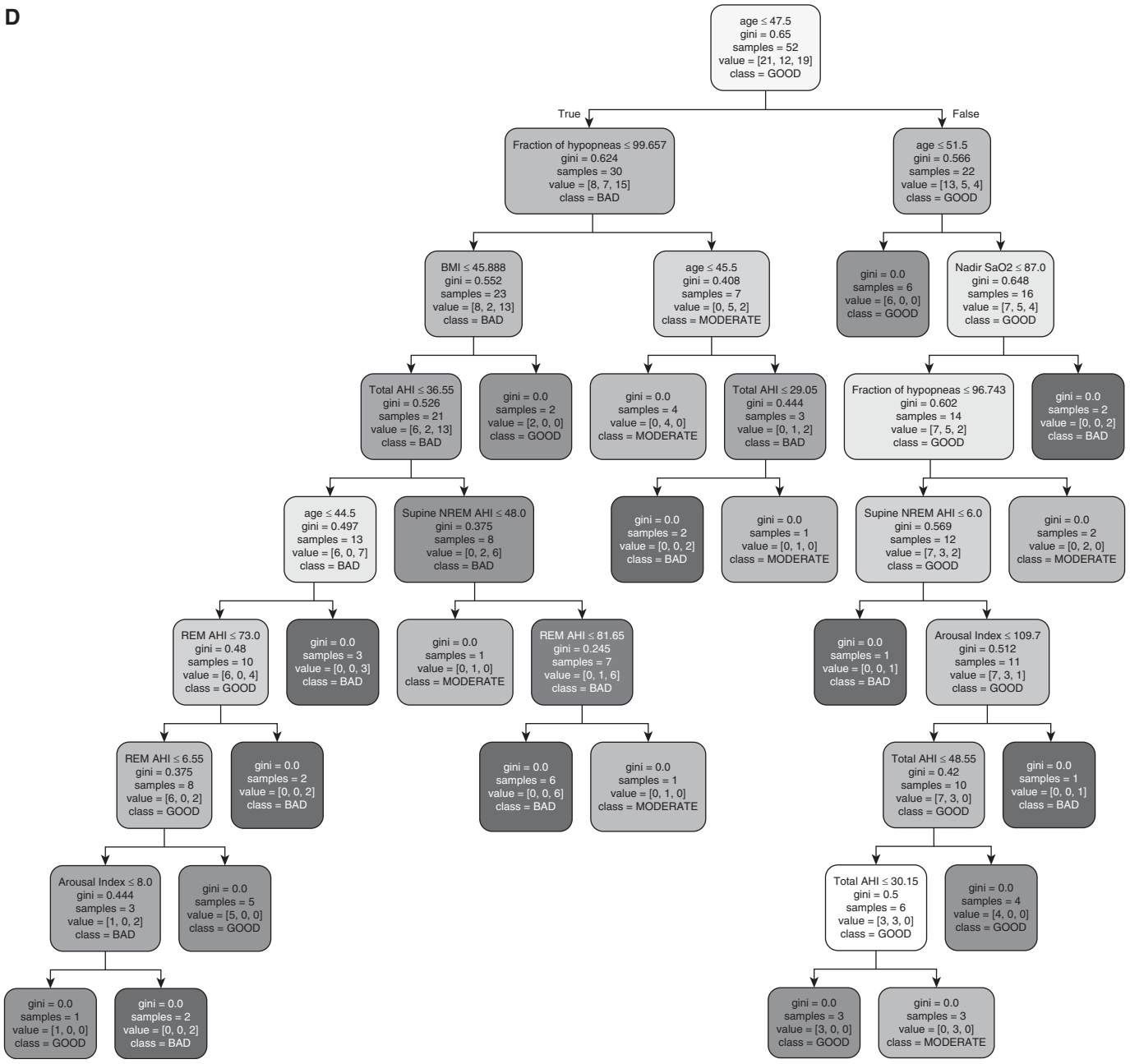


Figure 2. (*Continued*).

terms of clinical characteristics such as age and BMI. Thus, given that people without OSA who are overweight or have obesity tend to have differences in their endotypic traits, such as enhanced pharyngeal muscle responsiveness during sleep (64), the inclusion of control subjects with clinical characteristics closer to those of the patient population with OSA will be insightful for future investigations into the role of endotypic traits on OSA severity.

Conclusions

This study demonstrates that OSA endotypes are important contributors to PSG-defined OSA severity categories. The four traits can interact in multiple ways to either cause or prevent OSA. In addition, this initial work highlights the potential to use standard clinical and polysomnographic variables to estimate at least two of the four key OSA endotypes. These novel approaches may be useful to advance OSA pathophysiology and have the potential to be used to help identify and tailor targeted therapies for people with OSA. ■

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