ORIGINAL RESEARCH

Relationship between Symptom Profiles and Endotypes among Patients with Obstructive Sleep Apnea

A Latent Class Analysis

Wan-Ju Cheng[1,3,5], Eysteinn Finnsson[6], Eydís Arnardóttir[6], Jón S. Ágústsson[6], Scott A. Sands[7], and Liang-Wen Hang[2,4]

[1]Department of Psychiatry and [2]Sleep Medicine Center, Department of Pulmonary and Critical Care Medicine, China Medical University Hospital, Taichung, Taiwan; [3]Department of Public Health and [4]School of Nursing & Graduate Institute of Nursing, China Medical University, Taichung, Taiwan; [5]National Center for Geriatrics and Welfare Research, National Health Research Institutes, Miaoli, Taiwan; [6]Nox Research, Nox Medical ehf, Reykjavík, Iceland; and [7]Division of Sleep and Circadian Disorders, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

ORCID IDs: 0000-0003-4510-7584 (W.-J.C.); 0000-0003-3237-5491 (L.-W.H.).

Abstract

Rationale: Obstructive sleep apnea (OSA) is a heterogeneous syndrome with various endotypic traits and symptoms. A link among symptoms, endotypes, and disease prognosis has been proposed but remains unsupported by empirical data.

Objectives: To link symptom profiles and endotypes by clustering endotypic traits estimated using polysomnographic signals.

Methods: We recruited 509 patients with moderate to severe OSA from a single sleep center. Polysomnographic data were collected between May 2020 and January 2022. Endotypic traits, namely arousal threshold, upper airway collapsibility, loop gain, and upper airway muscle compensation, were retrieved using polysomnographic signals during non–rapid eye movement periods. We used latent class analysis to group participants into endotype clusters. Demographic and polysomnographic parameter differences were compared between clusters, and associations between endotype clusters and symptom profiles were examined using logistic regression analyses.

Results: Three endotype clusters were identified, characterized by high collapsibility/loop gain, low arousal threshold, and low compensation, respectively. Patients in each cluster exhibited similar demographic characteristics, but those in the high collapsibility/loop gain cluster had the highest proportion of obesity and severe oxygen desaturation observed in polysomnographic studies. The low compensation cluster was characterized by fewer sleepy symptoms and exhibited a lower rate of diabetes mellitus. Compared with the excessively sleepy group, disturbed sleep symptoms were associated with the low arousal threshold cluster (odds ratio, 1.89; 95% confidence interval, 1.16–3.10). Excessively sleepy symptoms were associated with the high collapsibility/loop gain cluster (odds ratio, 2.16; 95% confidence interval, 1.39–3.37) compared with the minimally symptomatic group.

Conclusions: Three pathological endotype clusters were identified among patients with moderate to severe OSA, each exhibiting distinct polysomnographic characteristics and clinical symptom profiles.

Keywords: arousal threshold; collapsibility; compensation; loop gain; phenotype

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Correspondence and requests for reprints should be addressed to Liang-Wen Hang, M.D., Ph.D., Sleep Medicine Center, Department of Pulmonary and Critical Care Medicine, China Medical University Hospital, 2 Yude Road, Taichung 40447, Taiwan. E-mail: lungwen.hang@gmail.com.

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Obstructive sleep apnea (OSA) is a common sleep breathing disorder characterized by repetitive apneas and hypopneas during sleep. OSA is diagnosed if the apnea–hypopnea index (AHI) is ⩾5 events per hour, but various symptom profiles, endotypic traits, and treatment outcomes have been observed in patients with OSA (1). In other words, OSA is a heterogeneous condition, and identifying pathological endotypes is crucial for effective treatment (2).

The most frequently recognized endotypic traits of OSA are high upper-airway collapsibility, low muscle compensation, high loop gain, and low arousal threshold (3, 4). To measure these endotypic traits simultaneously using noninvasive procedures, Sands and colleagues developed "phenotyping using polysomnography" (PUP) (5), a tool that was further developed as a cloud-based application (6). In the PUP method, endotypic traits are quantified by estimating ventilatory drive at different conditions by using a breath-by-breath analysis. This method enables a population-scale analysis of OSA endotypic traits and generates several endotypic measurements simultaneously. Although different combinations of endotypic traits have been suggested in patients with OSA, the interaction between these traits has rarely been studied.

Patients with OSA present to sleep clinics with various symptoms. International studies have identified three major symptom clusters: disturbed sleep, excessively sleepy, and minimally symptomatic (7–9). The excessively sleepy subtype exhibited increased risks of heart failure, cardiovascular disease, and coronary heart disease (10, 11). A smaller study observed an increased risk of cardiovascular disease in patients with excessive sleepiness combined with disturbed sleep symptoms compared with patients with minimal symptoms (12). Another cohort found an association of cardiovascular risk with hypoxic burden rather than symptom profiles (13). Among patients who were adherent to continuous positive airway pressure treatment, those who were excessively sleepy had an increased risk of cardiovascular mortality (14). Although researchers have sought to develop personalized treatment based on pathophysiology and symptomatology, the link between endotypic traits and symptom profiles has not been clarified.

This study aimed to cluster patients with OSA according to multiple endotypic traits and examine the symptom profiles and demographic, anthropometric, and polysomnographic characteristics of patients in each endotype cluster.

Methods

Participants

We prospectively enrolled patients aged ⩾20 years who were referred by physicians to the Sleep Center of China Medical University Hospital, Taiwan, for diagnostic polysomnography. The indications included snoring, assessment of OSA, hypersomnia, insomnia, parasomnias, and periodic limb movement disorders. A total of 509 patients had an AHI ⩾15/h and central apnea index <5/h and signed informed consent forms between April 2020 and January 2022. Demographic data were retrieved from medical charts, and patients self-reported physical illnesses and symptoms through a structured questionnaire before undergoing polysomnography. The questionnaire was similar to that used in the Sleep Apnea Global Interdisciplinary Consortium study cohort, which included Taiwanese participants (7). The participants self-reported if they were diagnosed with hypertension, diabetes mellitus, or cardiovascular diseases. This study was approved by the institutional review board of China Medical University Hospital (CMUH109-REC3-018).

Polysomnographic Study

Patients arrived at the sleep center before 11:00 P.M., and their blood pressure, pulse rate, neck and waist circumferences, and body weight and height were measured by technicians before polysomnography. The studies were performed using an NOX A1 polysomnography system (Nox Medical). Sleep staging and respiratory events were scored manually by certified sleep technicians. In this study, obstructive apnea was defined as the cessation of airflow through the nose with paradoxical chest and abdominal movements, and hypopnea was defined as a ⩾30% reduction in nasal pressure with paradoxical chest and abdominal movements, resulting in a desaturation of ⩾4% of oxygen saturation (Sp_{O_2}) according to the American Academy of Sleep Medicine recommended definition (15). Hypoxic burden was estimated by calculating the area under the Sp_{O_2} curve, with the pre-event Sp_{O_2} as the baseline (16).

Endotyping Using Polysomnography

Four endotypic traits, namely arousal threshold, upper-airway collapsibility, loop gain, and upper-airway muscle compensation, were estimated using the PUP method (5, 17) and a validated cloud-based Python application (Figure E1 in the data supplement) (6). The method derives OSA endotypes from polysomnographic data (including flow, scored electroencephalography, and scored respiratory events) by fitting a first-order model of the chemoreflex feedback system to the measured ventilation signal. The fitted model can be used to derive an

Table 1. Medians and IQR of endotypic trait values of clusters derived from latent class analysis ($N = 509$)

Endotype Description	Total ($N = 509$)	Cluster 1 ($n = 161$): High Collapsibility/Loop Gain	Cluster 2 ($n = 163$): Low Arousal Threshold	Cluster 3 ($n = 185$): Low Compensation
Arousal threshold, %	139.0 (58.3)	192.9 (56.3)	115.3 (15.7)	139.3 (27.5)
Collapsibility ($1 - V_{passive}$), %	14.9 (31.6)	54.1 (34.6)	5.7 (6.7)	12.0 (13.0)
Loop gain	0.57 (0.23)	0.73 (0.21)	0.53 (0.19)	0.51 (0.16)
Compensation, %	−3.6 (27.4)	−2.77 (23.0)	7.54 (8.4)	−20.0 (24.1)

Definition of abbreviations: IQR = interquartile range; $V_{passive}$ = percentage of ventilation at eupneic drive.
All four endotypic traits were significantly different among the three clusters by Kruskal–Wallis test. Pairwise analysis *t* tests showed significant results except that loop gain was not significantly different between clusters 2 and 3 ($P = 0.10$).

Table 2. Demographic, anthropometric, and polysomnographic characteristics of the three endotype clusters

Endotype Description	Cluster 1 ($N = 161$): High Collapsibility/ Loop Gain	Cluster 2 ($N = 163$): Low Arousal Threshold	Cluster 3 ($N = 185$): Low Compensation
Demographic and anthropometric characteristics			
Age, yr	43.4 ± 10.7	43.2 ± 11.5	43.5 ± 12.2
Female sex	17 (10.6%)	28 (17.2%)	25 (13.5%)
Body mass index, kg/m^2*	31.4 ± 5.5	30.5 ± 6.6	30.0 ± 13.4
Neck circumference, cm*	40.8 ± 4.0	40.2 ± 12.2	39.1 ± 3.4
Waist circumference, cm*	101.9 ± 11.3	98.9 ± 11.1	96.5 ± 13.9
Epworth Sleepiness Scale score	11.6 ± 5.3	9.8 ± 4.5	10.1 ± 4.8
Comorbidities			
Hypertension	57 (35.4%)	61 (37.9%)	59 (32.1%)
Diabetes mellitus*	27 (17.1%)	18 (11.3%)	14 (7.8%)
Cardiovascular disease	16 (10.3%)	10 (6.4%)	14 (7.8%)
Polysomnographic characteristics			
Apnea–hypopnea index, h^{-1}*	69.3 ± 22.1	28.1 ± 15.4	37.6 ± 17.5
REM apnea–hypopnea index, h^{-1}*	61.0 ± 24.6	47.4 ± 19.8	40.6 ± 23.9
Non-REM apnea–hypopnea index, h^{-1}*	71.0 ± 22.4	23.0 ± 17.7	36.7 ± 18.0
Hypopnea fraction, %*	22.6 ± 20.7	61.8 ± 25.2	48.3 ± 26.4
Time with $Sp_{O_2} \leqslant 90\%$, %*	35.2 ± 21.7	8.7 ± 11.5	13.0 ± 15.1
Time in bed, min*	387.1 ± 24.7	395.9 ± 25.0	393.4 ± 24.3
Total sleep time, min*	317.8 ± 53.3	331.7 ± 50.7	320.4 ± 54.5
Sleep efficiency, %	82.1 ± 12.4	83.7 ± 11.4	80.5 ± 13.0
Stage 1 sleep, %*	52.9 ± 21.5	29.2 ± 17.0	37.3 ± 17.1
Stage 2 sleep, %*	29.1 ± 18.5	48.7 ± 14.6	42.6 ± 15.3
Slow wave sleep, %*	0.9 ± 2.8	2.1 ± 5.0	1.7 ± 3.5
REM sleep, %*	17.1 ± 6.4	20.0 ± 7.0	18.4 ± 6.9
REM sleep latency, min	117.7 ± 57.1	109.8 ± 57.8	118.6 ± 62.0
Oxygen desaturation index, h^{-1}*	66.7 ± 21.7	25.6 ± 14.5	34.2 ± 17.5
Hypoxic burden, min%/h*	321.4 ± 172.2	76.2 ± 73.9	122.5 ± 92.0
Arousal index, h^{-1}*	64.0 ± 22.0	39.1 ± 19.0	41.9 ± 16.3
Periodic limb movement index, h^{-1}*	2.0 ± 6.7	7.0 ± 16.2	6.1 ± 12.2
Obstructive apnea duration in REM*	34.1 ± 13.4	22.0 ± 9.9	28.4 ± 14.8
Obstructive apnea duration in non-REM*	28.0 ± 7.0	18.9 ± 7.8	24.6 ± 8.4

Definition of abbreviations: REM = rapid eye movement; Sp_{O_2} = oxygen saturation.
Values presented as means ± standard deviation where applicable.
*$P < 0.05$ on χ^2 or Kruskal–Wallis tests.

estimate of the breath-wise chemical drive during sleep. The arousal threshold is defined as the estimated chemical drive right before scored electroencephalographic arousals (18). Loop gain is derived directly from the fitted model and is reported as the open loop gain at one cycle per minute. Collapsibility is calculated as 1 minus the percentage of ventilation at eupneic drive. Therefore, a large value of collapsibility in this study implies a more collapsible upper airway. Upper-airway muscle compensation is calculated by subtracting the percentage of ventilation at eupneic drive from the percentage of ventilation at arousal threshold (i.e., percent eupnea). Only non–rapid eye movement (REM) epochs were included for endotype estimation.

Statistical Analysis

Clustering endotypes. Clustering was performed using latent class analysis (19), which groups participants into mutually exclusive clusters. In clustering analysis, the four endotypic traits were dichotomized by median into high- and low-value groups (5). We attempted solutions for one to six clusters, and the number of clusters with the lowest Bayesian information criterion (BIC) and Akaike information criterion values was considered optimal (19). We have also performed clustering with continuous variables of the four endotypic traits using latent profile analysis, and the optimal number of clusters was considered based on BIC and bootstrap likelihood ratio tests (20). A bootstrap likelihood ratio test was used to choose the number of classes (21). We examined differences in demographic characteristics, anthropometric characteristics, and polysomnographic parameters between the endotype clusters using χ^2 tests for categorical variables and Kruskal–Wallis tests for continuous variables.

Clustering symptom profiles. To examine the relationship between endotypes and symptom profiles, we further generated symptom clusters by using a latent class analysis with three predefined clusters according to previous studies (7, 22). Scores on the Epworth Sleepiness Scale (ESS) were used for symptom clustering, along with 16 symptoms, namely headache upon awakening, perspiring heavily at night, restlessness during sleep, falling asleep involuntarily, falling asleep while watching television, taking naps, sleepiness during the day, feeling rested upon awakening, difficulty falling asleep, difficulty maintaining sleep, early awakening, disturbance caused to partner by snoring, cessation of breathing observed by others, physical tiredness during the day, sudden waking up and inability to breathe, and frequent dozing while driving. Symptom variables are categorized for clustering purposes. Patients were

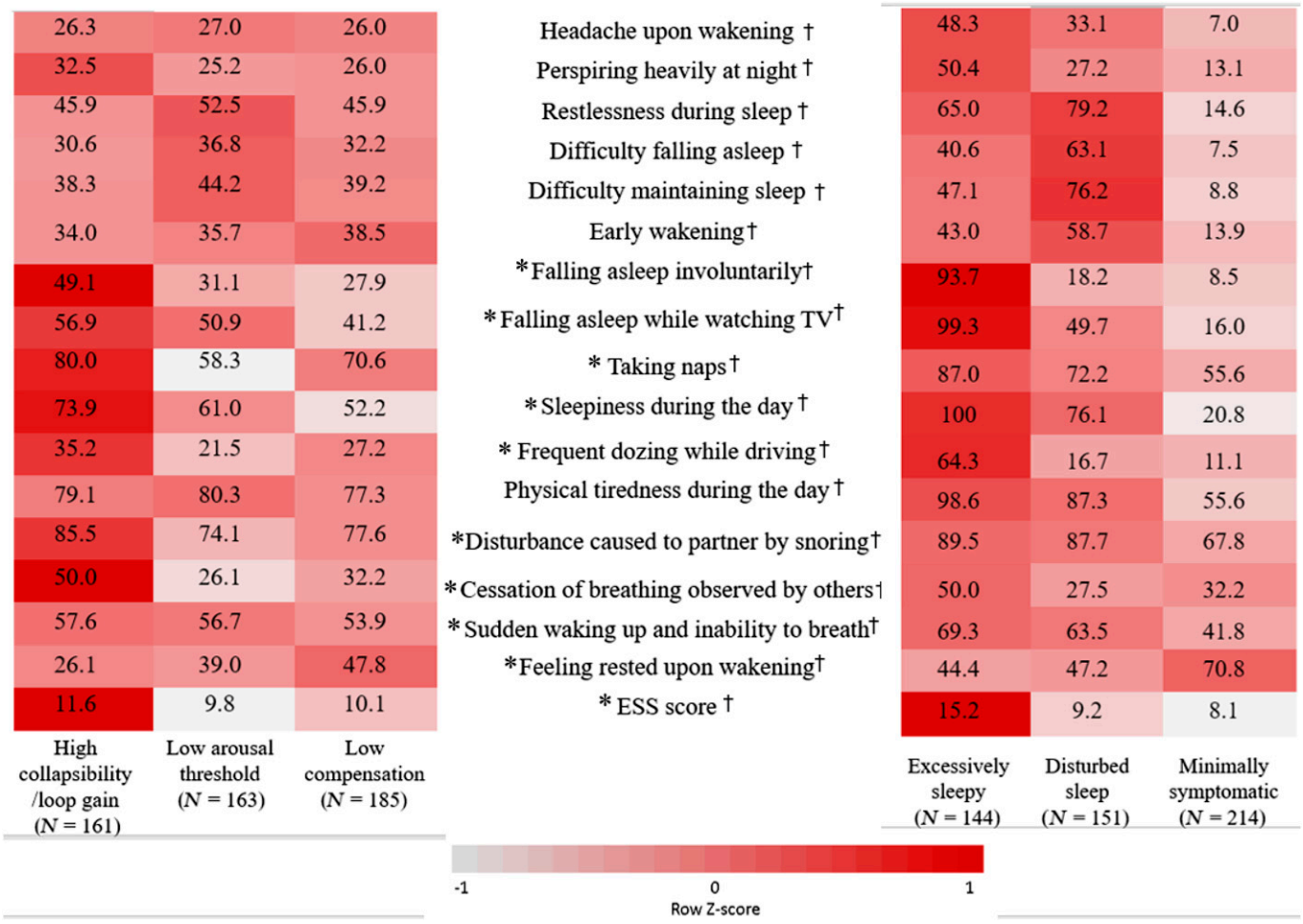

Figure 1. Symptom profiles of the endotype and symptom clusters. The relative differences in symptoms among clusters are indicated by the color scale, which represents the standardized symptom proportion. Brighter red indicates higher relative symptom burden. Numbers within the cells indicate the proportion of positive symptoms and the mean ESS score. Significant differences ($P < 0.05$) between endotype clusters by χ^2 or Kruskal–Wallis tests are indicated by asterisks, and differences between symptom clusters are indicated by daggers. ESS = Epworth Sleepiness Scale.

categorized into four groups according to ESS scores: 0–5, 6–10, 11–15, and >15 (23). For the 16 symptoms, participants reporting symptoms at least once per week were classified as positive for a given symptom; missing responses or individuals responding "don't know" or an incidence of less than once per week were classified as negative for the corresponding symptom (7).

Endotypes and symptom profile association analysis. We used multivariate logistic regression models to examine the association between the three symptom and endotype clusters. *Post hoc* pairwise comparison with Bonferroni adjustment was performed to assess whether the symptom cluster was predictive of belonging to a specific endotype cluster. Additionally, adjustments were made for age, sex, body mass index, and AHI. The 16 symptom proportions and ESS scores were standardized, and a heat map was generated to visualize symptom profiles in the three endotype and symptom clusters. SAS software (version 9.4; SAS Institute) was used for all the analyses, and the significance level was set at $P < 0.05$.

Results

Endotype Clustering

In the latent class analysis of the 509 participants, the optimal result was a three-cluster solution (BIC = 94.9; Table E1). The mean probabilities of belonging to a cluster were all higher than 0.7, and the cluster sample proportion was ⩾5%. Based on the model fit statistics, the optimal number of clusters identified through latent profile analysis was four or five (*see* Table E1). Table 1 presents the endotypic characteristics of the three clusters. Values for the four endotypic traits were all significantly different among the three endotype clusters on Kruskal–Wallis tests and pairwise comparisons. The first cluster had the highest arousal threshold, collapsibility, and loop gain. The second cluster exhibited the lowest arousal threshold and collapsibility and the highest compensation. The third cluster was characterized by a low compensation with a medium arousal threshold and collapsibility. We designated the three clusters as high collapsibility/loop gain, low arousal

Table 3. Crude and adjusted ORs and 95% CIs of logistic regression models examining the association between symptom and endotype clusters

	Model 1				Model 2			
Symptom Cluster	**OR**	**95% CI**	***P* Value**	**Adjusted *P* Value***	**OR**	**95% CI**	***P* Value**	**Adjusted *P* Value***
High collapsibility/loop gain cluster								
Excessively sleepy vs. minimally symptomatic	2.16	1.39–3.37	<0.01	<0.01	1.52	0.77–2.99	0.23	0.69
Disturbed sleep vs. minimally symptomatic	0.85	0.53–1.37	0.51	1.00	0.89	0.46–1.71	0.72	1.00
Disturbed sleep vs. excessively sleepy	0.39	0.24–0.65	<0.01	<0.01	0.58	0.28–1.22	0.15	0.45
Low arousal threshold cluster								
Excessively sleepy vs. minimally symptomatic	0.84	0.52–1.35	0.47	1.00	1.30	0.74–2.29	0.36	1.00
Disturbed sleep vs. minimally symptomatic	1.59	1.03–2.46	0.04	0.11	1.82	1.09–3.01	0.02	0.06
Disturbed sleep vs. excessively sleepy	1.89	1.16–3.10	0.01	0.03	1.39	0.77–2.52	0.27	0.82
Low compensation cluster								
Excessively sleepy vs. minimally symptomatic	0.54	0.34–0.85	0.01	0.02	0.62	0.38–0.99	0.045	0.14
Disturbed sleep vs. minimally symptomatic	0.73	0.48–1.12	0.15	0.46	0.70	0.45–1.08	0.11	0.32
Disturbed sleep vs. excessively sleepy	1.36	0.83–2.22	0.22	0.67	1.13	0.67–1.89	0.65	1.00

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
Model 1: crude model; model 2: adjusted for age, sex, body mass index, and apnea–hypopnea index.
*Bonferroni-adjusted *P* values.

threshold, and low compensation clusters, respectively. Table E2 displays the description of the four-cluster solution resulting from the latent profile analysis. The findings indicate the presence of a cluster with a high collapsibility/loop gain and another cluster with a low arousal threshold, as well as two clusters with low compensation and varying levels of arousal threshold. For ease of analysis, we used the three-cluster solution from the latent class analysis in subsequent analyses.

Demographic, Anthropometric, and Polysomnographic Characteristics

The three endotype clusters did not differ in age and sex distribution (Table 2). The high collapsibility/loop gain cluster had a higher body mass index and greater neck and waist circumferences than the other two clusters. The high collapsibility/loop gain endotype cluster also had a higher prevalence of diabetes mellitus, but the prevalences of hypertension and cardiovascular diseases were not significantly different among the three clusters. AHI, respiratory event duration, oxygen desaturation index, time with $Sp_{O_2} \leqslant 90\%$, and hypoxic burden were significantly higher in the high collapsibility/loop gain cluster, whereas the low arousal threshold cluster had the highest hypopnea fraction (hypopnea count/apnea and hypopnea count). The low arousal threshold cluster also had a sleep architecture within the normal expected range, whereas the high collapsibility cluster experienced REM sleep deprivation and the highest percentage of stage 1 sleep.

Symptom Profiles of the Endotype Clusters

The right panel of Figure 1 illustrates symptom profile clustering results. The first cluster ($n = 144$) exhibited severe daytime sleepiness, snoring, and moderate insomnia. The second cluster ($n = 151$) experienced prominent insomnia symptoms and restlessness and moderate sleepiness and snoring. The third cluster ($n = 214$) had minimal symptoms. We named the three clusters excessively sleepy, disturbed sleep, and minimally symptomatic, respectively. Demographic, anthropometric, and polysomnographic characteristics of the three symptom clusters are displayed in Table E3. Symptom profiles of the three endotype clusters are displayed in the left panel of Figure 1. The *z*-score heat map revealed a similar symptom profile between the excessively sleepy symptom cluster and the high collapsibility/loop gain endotype as well as between the disturbed sleep cluster and the low arousal threshold endotype. The exact case number in each endotype and symptom cluster matrix is presented in Table E4.

The logistic model revealed that, compared with the minimally symptomatic symptom cluster, the excessively sleepy symptom cluster was negatively associated with the low compensation endotype cluster (odds ratio [OR], 0.54; 95% confidence interval [CI], 0.34–0.85; Table 3) and positively associated with the high collapsibility/loop gain cluster (OR, 2.16; 95% CI, 1.39–3.37). The disturbed sleep symptom cluster was positively associated with the low arousal threshold endotype cluster (OR, 1.89; 95% CI, 1.16–3.10) compared with the excessively sleepy cluster. Compared with the excessively sleepy symptom cluster, the disturbed sleep symptoms cluster was negative associated with the high collapsibility/loop gain cluster (OR, 0.39; 95% CI, 0.24–0.65), but the association was not significant after adjustment.

Discussion

This is the first study to compare demographic, anthropometric, and polysomnographic characteristics and symptom profiles between different endotype clusters among patients with OSA. The three identified endotype clusters were characterized by *1*) high collapsibility combined with high loop gain and high arousal threshold, *2*) low arousal threshold combined with low collapsibility and high compensation, and *3*) low upper-airway compensation. The high collapsibility/loop gain cluster was associated with obesity and disturbed sleep architecture in

polysomnographic studies and had a symptom profile that coincided with the excessively sleepy symptom cluster. The low arousal threshold cluster had a high hypopnea fraction in polysomnographic studies and had a subjective symptom profile that coincided with the disturbed sleep symptom cluster. The low compensation cluster exhibited a symptom profile between the first two clusters.

Several studies have sought to identify different subtypes of OSA, with many including demographic data such as age and sex in their grouping models (24–26). In our study, no differences in age, sex, or cardiovascular comorbidities were observed among the three endotype clusters. We contend that the pathology of OSA, as represented by endotypes, is not dependent on demographic characteristics. Obesity and diabetes mellitus were more prevalent in the high collapsibility/loop gain endotype cluster. This may be because obese patients have a more compromised upper-airway structure as a result of redundant soft tissues. Studies have reported that body weight loss reduces tongue fat and prevents collapse during sleep (27). Therefore, body weight control is a paramount choice of treatment for this endotype cluster.

One novel finding of this study was the overlap observed between symptom clusters and endotypes identified through polysomnographic signals during non-REM sleep periods. The severely disrupted sleep architecture in the high collapsibility/loop gain cluster may explain symptoms of excessive sleepiness. This endotype cluster also had the highest AHI and longest duration of Sp_{O_2} ⩽90%. The high arousal threshold in this endotype cluster prevents patients from cortical arousal before upper-airway collapse, leading to high hypoxic burden (28), which is associated with cardiovascular disease mortality (16).

Although the low arousal threshold endotype cluster had a better sleep architecture than the other two clusters, participants in this cluster reported the most symptoms of disturbed sleep. Patients with OSA who have insomnia symptoms tend to underestimate their sleep duration (29). Patients with comorbid OSA and insomnia exhibited a large discrepancy between their subjective and objective sleep durations (30). Another contributing factor is periodic limb movements, which were more frequent in the low arousal threshold cluster than in the high collapsibility cluster and were associated with sleep misperception (31). Insomnia results in conditioned cortical arousal, unstable breathing patterns, and inadequate upper-airway muscle recruitment (32). Cognitive behavioral therapy for insomnia is therefore recommended for improving insomnia in patients with OSA (33). Cognitive behavioral therapy could be especially beneficial to those with low arousal threshold or comorbid insomnia (34) given the association between low arousal threshold and disturbed sleep symptoms observed in this study. Studies have reported that treating low arousal threshold with hypnotics improved sleep efficiency but did not consistently reduce AHI (35–37). In our study, the low arousal threshold endotype cluster did not have severe upper-airway pathologies and may respond favorably to treatments targeting low arousal threshold. However, we must emphasize that we used oxygen desaturation criteria without the consideration of cortical arousals for hypopnea scoring, and a desaturation of ⩾4% rather than 3%. Our approach may have led to an underestimation of AHI, especially in the low arousal threshold cluster compared with the other two clusters.

The goal of subtyping patients with OSA is to enable precise treatment and reduce comorbidities. Edwards and colleagues (1) proposed three subtypes linked by endotypic traits, symptom profiles, and treatment. In our study, the high collapsibility/loop gain endotype cluster and low arousal threshold endotype cluster were consistent with excessively sleepy and disturbed sleep symptom groups, respectively. Nevertheless, the low compensation endotype cluster showed a symptom profile between the high collapsibility and low arousal threshold clusters. The negative compensation value in this group suggests a negative effort dependence (38) and very poor upper-airway muscle recruitment function. Compared with endotypes estimated by polysomnography in a multiethnic study (39), our participants had similar arousal threshold, collapsibility, and loop gain values but a low compensation. We suggest that low compensation may be a unique characteristic of our study participants of Southeast Asian ethnicity. Combining noradrenergic agents with anticholinergic agents improves upper-airway function during sleep in patients with OSA (40), and the effectiveness of these agents in this cluster is promising.

The strength of this study was that we used endotypic traits derived from polysomnographic signals during non-REM sleep periods, and we linked symptomatology with pathology. However, there are limitations. First, the endotypes were dichotomized based on the median, which was determined by the distribution of the sample in this study. Hence, the results may not be directly applicable to other study populations. The median-split method has been used in the original PUP method to determine its validity (5) and in a multiethnic large-scale study (39). The median values of endotypic traits in this study were similar to those reported in the previous studies, with the exception of lower compensation. The low compensation cluster observed in this study may represent a unique group of Asian patients with OSA. Second, the endotypic traits were estimated only during non-REM sleep to avoid confounding physiological changes during REM sleep on the reported endotypic traits. These include reductions in loop gain and upper-airway compensation during REM sleep compared with the values derived from non-REM sleep (36, 41). Nevertheless, the effect of REM sleep on endotypes is relatively small compared with between-subject variability (39). Furthermore, during REM sleep, ventilation is not under the sole regulation of the chemical control system, and therefore it is not clear how well the first-order chemical feedback model fitting is able to capture respiratory dynamics during REM sleep. Third, the study participants were all of Asian ethnicity, a group in whom anatomical compromise has been observed to be a predominant factor for OSA compared with European populations (42). Hence, the results may not apply to patients of other ethnicities.

In conclusion, we identified three endotype clusters that are linked with specific symptom profiles. This linkage suggests not only that OSA is a heterogeneous disease but also that the pathological mechanisms of OSA may entail different symptom profiles, treatments, and comorbidities. Based on our research findings, patients who present symptoms of disrupted sleep may experience greater therapeutic benefits from treatment options that increase the arousal threshold

compared with patients who experience excessive sleepiness (43). In contrast, the latter group may respond better to treatments that address high collapsibility/loop gain, such as continuous positive airway pressure.

Given that the endotype and symptom profiles match only moderately in this study, future studies are required to examine whether these endotype clusters are replicable in other populations and whether endotype or symptom profiles are better predictive of treatment outcomes and morbidities. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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