Online Data Supplement:

Polysomnographic phenotypes in obstructive sleep apnea and their cardiovascular implications

Andrey V. Zinchuk, Sangchoon Jeon, Brian B. Koo, Xiting Yan, Dawn M. Bravata, Li Qin, Bernardo J. Selim, Kingman P. Strohl, Nancy S. Redeker, John Concato, Henry K. Yaggi

Comprehensive methods and additional results.

The cohort and non-polysomnographic measures

The Determining Risk of Vascular Events by Apnea Monitoring (DREAM) study was designed to assess cardiovascular risk among veterans undergoing OSA evaluation. It consists of 2041 adults from three Veterans Affairs Centers (West Haven, CT; Cleveland, OH, and Indianapolis, IN) enrolled between 2000 and 2004, with follow up through 2012 [1].

Experienced and trained research staff, blinded to study hypotheses, manually abstracted data from the Veterans Affairs Medical Center electronic medical record. At baseline (i.e., time of the polysomnogram, PSG), demographic factors (e.g., age, sex, race, employment and eligibility for veteran affairs services), anthropometric factors (e.g., height, weight, blood pressure and oxygen saturation at rest), cardiovascular risk factors (e.g., cigarette smoking, total and high/low density lipoprotein levels, diabetes, antihypertensive medications), medical comorbidity, alcohol and drug use, medication use, Epworth sleepiness scale (ESS), and other data as detailed previously were entered into the database. [1] Charlson comorbidity index (CCI) was calculated for each patient [2]. Quantitative cardiovascular risk for each patient at enrollment was ascertained using the Framingham risk score [3], which includes age, sex, presence of diabetes, anti-hypertensive medication use, systolic blood pressure, smoking status, total cholesterol, and high density lipoprotein levels.

Continuous positive airway pressure (CPAP) use measures

This VA study population received treatment according to consensus guidelines [4], with the PAP appliance and supplies ordered by the institution and issued through a single respiratory home care company at each study institution. Importantly, orders for these services are documented in the electronic medical record. In addition, patients are followed closely for assessment of efficacy and treatment compliance through established sleep medicine and pulmonary clinics where positive airway pressure use is documented. Two physician-investigators, blinded to outcome status, categorized each patient's airway pressurization treatment use in categories of not ordered, no use, intermittent use, and continuous or "regular" use of positive airway pressure. For the purposes of these analyses, airway pressurization compliance was dichotomized into "regular use" or not. Regular CPAP use was defined as "evidence of continued use" documented by above providers or documentation of supplies refilled at least every 6 months based on VA's prosthetics records (analogous to VA pharmacy data and "refills"). Patient PAP use was assessed an average of 5 (range 3-8) years after enrollment.

Primary outcome

Primary outcome was defined as composite incidence of transient ischemic attack (TIA), stroke, acute coronary syndrome (ACS), or death from any cause. Because OSA is associated with both non-fatal cardiovascular events [5] and all-cause mortality [6], and to improve ability to identify smaller patient groups that may be at risk of adverse events [7] we elected to use this composite outcome. Analogous outcomes are commonly used in

cardiovascular observational and clinical trial studies [8 9]. The primary outcome was adjudicated using VA's centralized electronic medical record and VA vital status file database information, as described previously [1]. In brief, the study's neurologist and cardiologist confirmed diagnoses of TIA, stroke, and ACS, via review of VA's medical record (inpatient and outpatient notes, and discharge summaries). ACS was defined according to guidelines of American College of Cardiology [10]. Ischemic stroke was defined as persistent focal neurological deficit of presumed ischemic origin lasting more than 24 hours [11], and TIA was defined as a focal neurological deficit of presumed ischemic origin lasting less then 24 hours [12]. The study cardiologist and neurologist graded all of patients as having a "definite," or "probable," or "unlikely" ACS, TIA, or stroke. A 30% random sample of the "definite" and "unlikely" events was reviewed by an internist and revealed excellent inter-observer variability (Cohen's Kappa of 0.88). All probable events were reviewed. The VA electronic medical record was used to capture events that may have occurred both in and outside of the VA system, given that patients with dual eligibility (VA and Medicare) tend to use the VA for either acute or post-acute care of stroke or myocardial infarction [13 14]. The participants were followed from baseline (time of polysomnogram) until development of stroke, acute coronary syndrome stroke, or death, with minimum of 3 years and maximum of 8 years of follow-up. The study was approved by the institutional review board at each study site.

Polysomnographic (PSG) measures and scoring

The details of the polysomnography and general scoring are described in a prior publication [1]. Polysomnograms were scored using American Academy of Sleep Medicine standards [15] at a centralized reading center (West Haven, CT). Aspects applicable to present report are described below. To assess the characteristics that various respiratory events may have in relationship to polysomnographic patient subtypes, respiratory events were classified by various states or associated events. Apnea was defined as complete or near complete reduction in thermocouple signal, lasting longer than 10 seconds. Apneas were classified as obstructive, mixed, or central, depending on presence or absence of respiratory effort and its relation to the interval of apnea, according to the American Academy of Sleep Medicine (AASM) recommended guidelines [15]. Mean duration and longest duration in seconds of apneas with above designation were recorded. Apneas were further classified as REM (rapid eye movement) or NREM (non-REM), if they occurred during each of these sleep states, respectively. Similarly, apneas were classified as supine or non-supine, depending on the position of the patient at the time of the event. Finally, apneas were classified as associated with an arousal only (without oxygen desaturation), associated with desaturation only (without an arousal), or combined (with both, arousal and desaturation). For the definition of apnea, oxygen desaturation was defined as ≥4%. Hypopneas were defined by ≥30% decrement in amplitude of nasal pressure flow signal for at least 10 seconds, and classified according to the association with an arousal only (without oxygen desaturation), association with a desaturation only (without an arousal), or as associated with a 4 % oxygen desaturation (with or without an arousal). Arousals were scored according to published guidelines [16]. Oxygen desaturation indices were

obtained for events of >2%, > 3%, > 4%, and > 5%, in both REM and NREM sleep. Time spent within a given range of oxygen saturation was recorded (60-69%, 70-79%, 80-89%, and >90%). We included patients on supplemental home oxygen in cluster analyses (7.2% of the analytic sample), and these patients underwent diagnostic polysomnography without supplemental oxygen, thus not affecting measurement of hypopneas. Their inclusion was felt to be important to represent the clinical population studied at the three centers. The number of shifts between sleep stages was also recorded, with sleep stages scored using 30-second epochs according to Rechtschaffen and Kales criteria [15]. Sleep architecture variables were noted as time in stages of NREM 1, NREM 2, NREM 3 and 4, and REM sleep, as well as number of shifts between stages. Epworth sleepiness scale was obtained at time of polysomnography.

Variable selection and transformation process and analytic sample

Data selection for analysis included two steps: variable selection (step 1) followed by case selection (step 2). This process was adopted to balance the loss of variables (impacting ability to identify important physiologic factors) and loss of sample size (impacting the power to detect clusters and their implications).

For step 1, 65 scored PSG variables were categorized into the domains of breathing disturbance, autonomic dysregulation, hypoxemia, and sleep architecture disturbance, according to the known mechanisms of cardiovascular consequences of obstructive sleep apnea (OSA) captured by PSG measures [17 18]. To ensure that clinically relevant

variables were included, and as an initial selection step, a review was conducted with practicing sleep clinicians at Yale Sleep Center. Clinically redundant variables (e.g., time in bed) were excluded if other variables chosen to reflect physiologic parameters (e.g., total sleep time and sleep efficiency) were included. Of the remaining variables, those with >5% of missing data (e.g., position related respiratory events) and categorical variables (e.g., snoring [yes/no]) were excluded, due to requirements of the cluster analysis methods. All index variables (e.g., obstructive apnea index) were normalized to total sleep time. Oxygenation variables (e.g., mean nocturnal saturation) were derived from measured values in REM and NREM sleep. Desaturation indices were consolidated into those >4% or 2-4% [19]. Time spent within a given range of desaturation was consolidated into that with <90% saturation or ≥90% [17]. AHI was calculated as the total number of apneas and hypopneas (defined as ≥30 % decrement in flow signal for at least 10 seconds associated with a 4% oxygen desaturation) per hour of sleep. Apnea hypopnea index (AHI) was not included in variable reduction or cluster analysis, given that it was the arithmetic composite of variables included already. A total of 29 variables (Table E1) were retained for variable reduction analysis.

Step 2 (case selection for the analytic sample) is described in the methods section of main manuscript. Notably, patients with missing data on any of the 29 variables were excluded from the analysis. Steps 1 and 2 produced an analytic sample without any missing data required for cluster analysis.

Variable reduction analysis

The objective of this step was to identify unique, interpretable PSG features with minimal correlation, while maintaining majority of the data variance of the 29 PSG variables. Variables were standardized with mean of zero and one standard deviation. For each domain (e.g., breathing disturbance), the VARCLUS procedure [20 21] was used to generate clusters of variables that are highly correlated within each cluster, and relatively independent across different clusters. In brief, the procedure is an iterative process that divides a large set of variables into several disjoint clusters. First, by performing principal component analysis on variables in each domain, two primary principal components with the highest eigenvalues are extracted and obliquely rotated: $PC_1 = \sum_{i=1}^{k} a_{1i}x_i$ and $PC_2 = \sum_{i=1}^{k} a_{2i}x_i$ where a_{1i} and a_{2i} are coefficients of variable x_i in two principal components PC_1 and PC_2, respectively. If a_{1i}>a_{2i}, then variable x_i is assigned to cluster 1, and otherwise it is assigned to cluster 2. The same process is repeated with the subgroup variables assigned to cluster 1 and cluster 2 separately. As process is repeated, more clusters are formed with increasing proportion of the total variance explained. Within each domain, selection of the minimum number of features (clusters, or individual variables), while explaining >75% of the total variance within the domain, was felt to result in clinically meaningful PSG features yet preserving much of data variance. For example, a dendrogram plot for the domain of “breathing disturbance” is shown in Figure E1a and can be interpreted as follows. Eleven polysomnographic variables explain 100% of the data variance (left side of the figure). As variables are grouped into clusters (variable reduction) the amount of variance explained decreases (moving toward the right of the figure), with 40% of the data

variance explained by two features: feature 1 composed of 4% hypopnea, combined hypopnea and arousal hypopnea indices and feature 2 of the remaining variables. A vertical line in Figure E1a shows that at a 75% variance explained threshold, 11 variables can be reduced to 6 features. Dendrograms for remaining domains are shown in Figures E1b-d.

To generate standardized scores for each variable cluster, we calculated principal component score to be used as a feature score within each domain. The features can be individual variables, or clusters of variables, depending on the amount of the variance threshold selected. The variable reduction analysis for all of the domains reduced 29 variables to 17 clinically interpretable features that explain 83% of the total data variance (Tables E2 and E3).

Patient based cluster analysis (patient "phenotypes")

K-means (centroid method) analysis using standardized feature scores was employed to generate patient clusters ("phenotypes"). Because K-means, in general, produces clusters that are less affected by outliers and presence of irrelevant clustering variables, and because it enables subjects to change cluster affiliation in the course of the clustering process, we elected this partitioning method for as opposed to the hierarchical clustering approach[22]. This method uses an iterative partitioning algorithm to classify subjects into pre-determined number of clusters (k), by minimizing the distance of observations from a center of each cluster based on the feature values. The

objective is to segment data so that within-cluster variation is minimized, and homogeneous groups of subjects are formed, based on the features employed [23]. This strategy was implemented with SAS procedure of PROC FASTCLUS [24].

To select the number of clusters, we used silhouette width, a commonly used cluster quality measure [25], as well as clinical interpretability [26]. Silhouette of a cluster is defined as average proximity of observations to other observations in the assigned cluster, vs. average proximity to observations in the nearest cluster to which it is not assigned. The maximal silhouette value is 1, and the minimal value is -1. Large values indicate good separation of most cluster members from members of other clusters, whereas negative values indicate indecisiveness/error of a given partition [25]. Silhouette values for cluster solutions (k = 2 – 9) are shown in Table E4. Given that our aim was to identify patient subgroups beyond traditional severity categorizations (none, mild, moderate, and severe), we focused on cluster numbers 5 - 9. A seven-cluster solution was selected based on a-priori criteria of a highest weighted average silhouette value and a non-negative lowest average silhouette value. Although a marked difference in average silhouette values was not found for 5, 6 and 7 cluster solutions, the lowest average silhouette value in the seven-cluster solution exhibited highest positive magnitude (suggesting least similarity to other clusters), and it enabled differentiation of patients based on contributions from periodic limb movements of sleep and hypopneas with hypoxia (in comparison to a 5 cluster solution).

The Jaccard coefficient, a measure of similarity of clusters between two samples, was used to assess cluster stability using 1000 bootstrap samples (Table E5) [27]. The coefficient ranges from 0 to 1, and a perfect match is represented by value of 1.

A heatmap and table of the standardized principal component feature scores for each cluster is shown below (Figure E3 or Table E7). Criteria for constructing the heatmap included assignment of red color to minimal, and yellow color to maximal, standardized principal component values within each domain for each cluster. Prevalence of cluster membership within each conventional AHI-based sleep apnea severity category (none/mild, moderate and severe) is shown in Figure E3.

Cross-sectional analysis of cluster characteristics (comorbidities)

Cross-sectional contrasts between clusters were performed using analysis of variance or X^2 tests, with Bonferroni correction for multiple comparisons. Summary of comorbidity prevalence for each cluster is noted in Table E7, including 95% confidence intervals (adjusted for multiple comparisons using Bonferroni correction) and the Wald test for differences among clusters. Significance level is p value < 0.05.

Association with primary outcome

The primary outcome distribution by cluster is shown in Table E8.

To assess relationship between OSA clusters and incident primary outcome, unadjusted Cox proportional-hazards models were used showing significance (log rank p-value <0.001), and remained significant after adjustment for multiple comparisons using false discovery rate. Cox-Snell residuals from the Cox proportional-hazards model was used to evaluate the overall fit of the model [28]. The cumulative hazard of the Cox-Snell residual model was linear, with approximate slope of 1 indicating a good fit. The Cox proportional hazards assumption for the model comparing each cluster to the "mild" group was confirmed using the cumulative hazard function. Cox proportional-hazards models were generated, including cluster membership, Framingham risk score, and CPAP use. We also performed analysis adjusting cluster membership, CPAP use and age, sex, smoking, BMI, alcohol use and ethnicity. Since our goal was to determine whether cluster membership had implications for incident CVD or death in addition to the baseline cardiovascular risk and given that FRS model exhibited better fit, similar hazard ratios (<10% difference) with narrower confidence intervals, we used the model incorporating FRS in further analyses.

We repeated the adjusted Cox proportional-hazard models using AHI severity categories only (without cluster membership), to assess whether risk of primary outcome was captured by this conventional OSA severity measure. Participants missing any component of the Framingham risk score were excluded from these analyses (n=1036). Given that a majority of the composite outcome for each cluster was all-cause mortality (see Table E8), a sensitivity analysis model using CCI, CPAP use, and cluster membership was generated (Table E9). CCI was categorized into three score

categories, representing 32% (CCI of 0), 42% (CCI of 1 to 2), and 26% (CCI of 3 or greater) of patients, respectively. Significant associations between the primary outcome and clusters found in the original adjusted model (cluster membership, CPAP use, Framingham risk score) persisted, along with an additional cluster, “NREM & poor sleep” exhibiting significantly increased risk (Table E9).

To assess whether continuous oxygen use in a small percentage of patients modified the impact of cluster membership on the primary outcome, we performed a sensitivity analysis including home oxygen use as a covariate in the model. Home oxygen use at baseline was associated with greater then 4-fold increase in risk of primary outcome. The magnitude of the hazard ratios for each cluster was mildly attenuated, with only the risk for “hypopnea & hypoxia” cluster changing statistical significance in terms of association with the primary outcome (HR of 1.70 95% CI of 0.99, 2.92, Table E10).

To assess the impact of analytic sample selection (n=1247), we compared the BMI, AHI, Framingham risk scores, Charlson comorbidity indices, and primary outcome between the analytic sample and excluded patients. No differences were found on any of the above measures (Table E11). We also performed a sensitivity analysis of the final model by addition of study center variable into the final model, which revealed no significant impact of study site on the primary outcome (HR 0.98, 95% CI (0.74, 1.30), p-value 0.904).

Finally, to assess whether the reference group played a role in the difference between AHI categories and cluster's association with primary outcome, we used various reference groups in evaluating AHI's association with the primary outcome in adjusted models (AHI variable, FRS and home oxygen use). We did not find significant associations with primary outcome when continuous AHI (p-value 0.2276) or three severity categories (none [AHI<5, reference] vs. mild [5≤AHI<15, p-value 0.4192], moderate [15≤AHI<30, p-value 0.1775] or severe [AHI≥30, p-value 0.2218]) were evaluated (data not shown).

Table E1. Variables (n=29) used to determine polysomnographic features for patient based cluster analysis, grouped by known domains pathophysiological mechanisms with implications for cardiovascular disease in OSA

Domain	Selected Variable
Breathing disturbance	OA index
	Mixed apnea index
	Central apnea index
	Apnea D4 index
	Apnea arousal index
	Combined apnea index
	Apnea REM index
	Apnea NREM index
	Hypopnea arousal index
	Hypopnea D4 index
	Original hypopnea index
Sleep architecture disturbance	Sleep latency (min)
	Sleep efficiency (%)
	Stage 1 (% of total sleep time, TST)
	Stage 2 (% of TST)
	Stage 3, 4 (% of TST)
	REM sleep (% of TST)
	Stage shifts index
Autonomic dysfunction	Total arousal index
	Respiratory arousal index
	Spontaneous arousal index
	PLMS index
Hypoxemia	T60-89% O_2 saturation index*
	T90-99% O2 saturation index*
	Mean nocturnal O_2 saturation
	Desaturation 2 to 4% index
	Desaturation > 4% index
	Mean wake O_2 saturation
	Lowest nocturnal O_2 saturation

All index variables represent number of events per hour of total sleep time (TST) unless otherwise noted. REM – rapid eye movement, PLMS – periodic leg movements of sleep, Apnea D4 or hypopnea D4 (apnea or hypopnea with 4% desaturation only and no arousal), Apnea arousal or Hypopnea arousal (apnea or hypopnea with an arousal only and no desaturation), Combined apnea (apnea with 4% desaturation and an arousal), Original hypopnea (hypopnea with 4% desaturation with or without arousal). * – minutes with O_2 saturation of 60-89% / minutes of TST, similar calculation for T90-99% saturation index.

Table E2a. Cluster structure for breathing disturbance domain with 79% of variance explained while maintaining minimal number of features (6) for each domain (n=1248).

Cluster (label) / Variable	**Variable**	***R^2 with cluster***		***Pearson Corr. With PC within a cluster***
		Own	**Next Closest**	
Cluster 1 (Apneas with desaturation)	OA index	0.926	0.205	0.962
	Apnea D4 index	0.381	0.086	0.618
	ComApnea index	0.867	0.089	0.931
	Apnea NREM index	0.942	0.226	0.970
Cluster 2 (Hypopneas with desaturation)	Hypopnea D4 index	0.627	0.013	0.792
	Original hypopnea index	0.627	0.049	0.792
Cluster 3 (Chemoreflex apneas)	MA index	0.682	0.146	0.826
	CA index	0.682	0.033	0.826
Variable 4	Apnea REM index	1.000	0.015	1.000
Variable 5	Hypopnea Arousal index	1.000	0.031	1.000
Variable 6	Apnea Arousal index	1.000	0.128	1.000

Apnea D4 – apnea with 4% desaturation but without arousal, ComApnea – Combined Apnea (apnea with 4% desaturation and arousal), Apnea Arousal – apnea with arousal but without desaturation. Hypopnea D4 and Hypopnea Arousal are defined in same manner as apneas, Original Hypopnea – hypopnea with 4% desaturation with or without arousal. OA, CA,MA – obstructive, central and mixed apneas respectively. REM – rapid eye movement, NREM – non-rapid eye movement.

Table E2b. Cluster structure for sleep architecture domain with 83% of variance explained while maintaining minimal number of features (4) for each domain (n=1248).

Cluster (label) / Variable	**Variable**	***R^2 with cluster***		***Pearson Corr. With PC within a cluster***
		Own	**Next Closest**	
Cluster 1 (Sleep fragmentation)	Sleep latency	0.7536	0.0158	0.868
	Sleep efficiency	0.7536	0.2656	-0.868
Cluster 2 (Light sleep measures)	Stage 1 %	0.8630	0.1284	0.929
	Stage 2 %	0.7437	0.0541	-0.862
	Stage shifts index	0.6940	0.1601	0.833
Variable 3	REM %	1.0000	0.0424	1.000
Variable 4	Stage 3 & 4 %	1.0000	0.0106	1.000

Table E2c. Cluster structure for autonomic dysfunction domain with 97% of variance explained while maintaining minimal number of features (3) for each domain (n=1248).

Cluster (label) / Variable	**Variable**	***R^2 with cluster***		***Pearson Corr. With PC within a cluster***
		Own	**Next Closest**	
Cluster 1 (Respiratory arousals)	Respiratory arousal index	0.947	0.024	0.973
	Total arousal index	0.947	0.100	0.973
Variable 2	Spontaneous arousal index	1.000	0.014	1.000
Variable 3	PLMS index	1.000	0.012	1.000

PLMS – periodic leg movements of sleep

Table E2d. Cluster structure for hypoxia domain with 86% of variance explained while maintaining minimal number of features (4) for each domain (n=1248).

Cluster (label) / Variable	**Variable**	***R^2 with cluster***		***Pearson Corr. With PC within a cluster***
		Own	**Next Closest**	
Cluster 1 (Time spent at < 90% saturation)	Mean nocturnal O_2 index	0.778	0.329	0.882
	T90-99% O_2 saturation index	0.930	0.237	0.964
	T60-89% O_2 saturation index	0.924	0.232	-0.961
Cluster 2 (Desaturation frequency)	Desaturation 2 to 4% index	0.682	0.003	0.826
	Desaturation > 4% index	0.682	0.193	0.826
Variable 3	Mean wake O_2 saturation	1.000	0.188	1.000
Variable 4	Lowest nocturnal O_2 saturation	1.000	0.299	1.000

Table E3. Seventeen polysomnographic features (middle column) resultant from the variable reduction procedure of the 29 variables (right column) grouped by domain.

Domain	Feature label (designation)	Selected Variable(s)
Breathing disturbance	Apneas with desaturations (BD1)	OA index Apnea D4 index Combined apnea index Apnea NREM index
	Hypopneas with desaturations (BD2)	Hypopnea D4 index Original hypopnea index
	Chemoreflex apneas (BD3)	Mixed apnea index Central apnea index
	Apnea arousal index	Apnea arousal index
	Apnea REM index	Apnea REM index
	Hypopnea arousal index	Hypopnea arousal index
Sleep architecture disturbance	Sleep fragmentation (SA1)	Sleep latency Sleep efficiency
	Light sleep measures (SA2)	Stage 1% Stage 2% Stage shifts index
	Slow wave sleep %	Stage 3, 4%
	REM sleep %	REM sleep %
Autonomic dysregulation	Respiratory arousals (AD1)	Respiratory arousal index Total arousal index
	Spontaneous arousal index	Spontaneous arousal index
	PLM index	PLM index
Hypoxia	Time spent at < 90% saturation (HY1)	T60-89% O_2 saturation index T90-99% O_2 saturation index Mean nocturnal O_2 index
	Desaturation frequency (HY2)	Desaturation 2 to 4% index Desaturation > 4% index
	Lowest nocturnal O_2 saturation	Lowest nocturnal O_2 saturation
	Mean wake O_2 saturation	Mean wake O_2 saturation

BD – breathing disturbance, HY – hypoxemia, AD – autonomic dysregulation, SA – sleep architecture disturbance domain cluster features.
REM – rapid eye movement, PLM – periodic leg movements, Apnea D4 or hypopnea D4 (apnea or hypopnea with 4% desaturation only and no arousal), Combined apnea (apnea with 4% desaturation and arousal), Original hypopnea (hypopnea with 4% desaturation with or without arousal).
The seventeen features retain 83% of data variance within the 29 individual variables.

Table E4. Silhouette values for the K-means cluster solutions (K = 2 - 9)

Cluster # solution / Silhouette value	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Weighted average silhouette	0.260	0.211	0.190	0.165	0.160	0.162	0.159	0.142
Lowest average silhouette	0.002	0.005	0.002	-0.037	-0.033	0.026	0.000	0.011

Table E5. Jaccard coefficient values for each cluster with 1000 bootstrap samples assessing cluster stability

Cluster	**Median**	**Mean**
A (mild)	0.952	0.934
B (PLMS)	0.671	0.704
C (NREM & arousal)	0.868	0.801
D (REM & hypoxia)	0.701	0.717
E (hypopnea & hypoxia)	0.681	0.684
F (arousal & poor sleep)	0.903	0.865
G (combined severe)	0.695	0.702

Table E6. Standardized values for 17 features for each patient cluster

Cluster/ Feature Mean (95% CI)*	**mild (A)**	**PLMS (B)**	**NREM & poor sleep (C)**	**REM & hypoxia (D)**	**hypopnea & hypoxia (E)**	**arousal & poor sleep (F)**	**combined severe (G)**	**MSR/MSE**	**RSQ/ (1-RSQ)**
N	533	119	186	168	75	42	124		
AHI†	7.5 (5.5,9.6)	13.6 (9.3,17.9)	24.0 (20.6,27.5)	25.1 (21.4,28.7)	47.6 (42.2,53.0)	72.6 (65.3,79.8)	82.4 (78.2,86.6)	394.87	
Apneas with desaturations (PC:ML1)	-0.52 (-0.59,-0.45)	-0.38 (-0.52,-0.23)	-0.09 (-0.20,0.03)	0.03 (-0.09,0.35)	0.16 (-0.02,0.35)	1.15 (0.90,1.40)	2.16 (2.02,2.31)	377.24	1.826
Hypopneas with desaturations (PC:ML2)	-0.35 (-0.43,-0.27)	-0.16 (-0.33,0.01)	-0.03 (-0.16,0.10)	0.11 (-0.03,0.25)	2.83 (2.62,3.04)	-0.04 (-0.32,0.24)	-0.14 (-0.31,0.02)	242.95	1.123
Chemoreflex apneas (PC:ML3)	-0.23 (-0.33,-0.12)	-0.20 (-0.42,0.02)	-0.02 (-0.19,0.16)	-0.12 (-0.31,0.06)	-0.12 (-0.39,0.16)	0.49 (0.11,0.86)	1.27 (1.06,1.49)	51.36	0.248
Apnea arousal index	-0.29 (-0.36,-0.22)	-0.13 (-0.27,0.02)	0.03 (-0.08,0.15)	-0.10 (-0.22,0.02)	-0.23 (-0.42,-0.05)	4.26 (4.01,4.50)	0.16 (0.02,0.30)	393.66	1.904
Apnea REM index	-0.26 (-0.35,-0.17)	-0.14 (-0.33,0.05)	-0.31 (-0.46,-0.15)	1.56 (1.40,1.73)	-0.29 (-0.54,-0.05)	-0.19 (-0.52,0.14)	-0.15 (-0.33,0.05)	128.36	0.652
Hypopnea arousal index	-0.23 (-0.32,-0.13)	-0.04 (-0.24,0.16)	0.59 (0.43,0.75)	-0.08 (-0.25,0.09)	0.19 (-0.07,0.44)	0.96 (0.62,1.30)	-0.33 (-0.53,-0.13)	36.50	0.161
Respiratory arousals (PC:AD1)	-0.65 (-0.72,-0.58)	-0.28 (-0.43,-0.13)	0.45 (0.34,0.57)	-0.19 (-0.31,-0.06)	0.57 (0.38,0.76)	1.57 (1.31,1.82)	1.76 (1.61,1.90)	360.86	1.746
Spontaneous arousal index	-0.11 (-0.21,-0.01)	-0.11 (-0.32,0.10)	1.15 (0.98,1.32)	-0.36 (-0.54,-0.18)	-0.12 (-0.39,0.15)	-0.10 (-0.46,0.26)	-0.55 (-0.76,-0.34)	69.44	0.354
PLM index	-0.26 (-0.35,-0.11)	2.51 (2.36,2.65)	-0.19 (-0.30,-0.08)	-0.23 (-0.35,-0.11)	-0.29 (-0.47,-0.11)	-0.32 (-0.56,-0.08)	-0.41 (-0.55,-0.27)	412.34	1.994
Sleep fragmentation (PC:SA1)	-0.25 (-0.35,-0.14)	0.16 (-0.06,0.39)	0.82 (0.64,1.00)	-0.38 (-0.57,-0.19)	0.05 (-0.24,0.33)	0.53 (0.15,0.91)	-0.02 (-0.24,0.21)	38.61	0.197

Light sleep measures (PC:SA2)	-0.39 (-0.48,-0.29)	-0.20 (-0.41,0.00)	0.87 (0.70,1.04)	-0.33 (-0.51,-0.16)	-0.13 (-0.39,0.13)	0.99 (0.64,1.35)	0.75 (0.55,0.96)	83.23	0.419
Stage 3, 4 %	0.21 (0.10,0.32)	-0.03 (-0.27,0.21)	-0.34 (-0.54,-0.15)	0.12 (-0.09,0.32)	0.01 (-0.29,0.31)	-0.29 (-0.69,0.11)	-0.41 (-0.65,-0.18)	12.84	0.061
REM sleep %	0.42 (0.32,0.52)	-0.05 (-0.26,0.16)	-0.56 (-0.73,-0.39)	0.42 (0.24,0.59)	-0.56 (-0.73,-0.39)	-0.67 (-0.94,-0.41)	-0.79 (-1.00,-0.58)	72.79	0.356
Time spent at < 90% saturation (PC:HY1)	0.39 (0.29,0.50)	0.05 (-0.16,0.27)	0.05 (-0.12,0.23)	-0.36 (-0.54,-0.17)	-0.79 (-1.07,-0.51)	0.26 (-0.10,0.63)	-0.95 (-1.16,-0.73)	56.28	0.264
Desaturation frequency (PC:HY2)	-0.64 (-0.72,-0.56)	-0.31 (-0.47,-0.13)	0.23 (0.10,0.37)	0.08 (-0.06,0.22)	1.36 (1.15,1.57)	0.89 (0.60,1.17)	1.46 (1.30,1.62)	245.63	1.192
Mean wake O_2 saturation	0.22 (0.11,0.33)	-0.23 (-0.47,0.01)	0.13 (-0.06,0.32)	-0.32 (-0.52,-0.11)	-0.36 (-0.66,-0.05)	0.06 (-0.35,0.46)	-0.31 (-0.54,-0.07)	12.95	0.058
Lowest nocturnal O_2 desaturation	0.48 (0.40,0.57)	0.02 (-0.17,0.21)	0.29 (0.14,0.44)	-1.32 (-1.48,-1.16)	-0.50 (-0.74,-0.26)	0.62 (0.31,0.94)	-0.66 (-0.84,-0.47)	150.0	0.693

PLMS – periodic leg movements of sleep, REM – rapid eye movement, MSR/MSE – regression mean square / mean square error, RSQ/(1 - RSQ), the ratio of between-cluster variance to within-cluster variance, NREM – non-REM, Apnea/hypopnea D4 (apnea/hypopnea with 4% desaturation only and no arousal), Combined apnea (apnea with 4% desaturation and arousal), Original hypopnea (hypopnea with 4% desaturation with or without arousal). DGT – desaturation greater then X, T90 - time spent at oxygen saturation of less than 90% divided by total sleep time (TST).

PC:SA1 – Principal component of sleep latency and sleep efficiency

PC:SA2 – Principal component of Stage 1, 2, Stage shifts %

PC:AD1 – Principal component of respiratory arousal and arousal indices

PC:ML1 – Principal component of obstructive apnea, apnea D4, combined apnea, apnea NREM indices

PC:ML2 – Principal component of Hypopnea D4, original hypopnea indices

PC:ML3 – Principal component of Mixed apnea and central apnea indices

PC:HY1 – Principal component of Mean nocturnal O_2 saturation, T90% index

PC:HY2 – Principal component of DGT2to4% and DGT<4% indices

* 95% CI is simultaneous 95% confidence interval for Bonferroni adjustment

† – AHI was not one of the features used for cluster analysis, values are not standardized.

Table E7. Baseline prevalence of comorbidities among the patient clusters

Condition prevalence (95% CI) / Cluster	**mild**	**PLMS**	**NREM & poor sleep**	**REM & hypoxia**	**hypopnea & hypoxia**	**arousal & poor sleep**	**combined severe**	**Wald P-value**
N	533	119	186	168	75	42	124	
OSA category	None/Mild		Moderate		Severe			
Hypertension	61.5% (57.3,65.6)	79.1% (70.8,85.6)	76.8% (70.1,82.3)	72.5% (65.2,78.7)	82.4% (72.2,89.4)	87.8% (74.5,94.7)	80.6% (72.8,86.7)	<.0001
Diabetes	24.0% (20.6,27.9)	36.5% (28.3,45.6)	36.5% (29.8,43.7)	35.9% (29.0,43.4)	41.3% (30.9,52.6)	41.5% (27.8,56.6)	33.1% (25.4,41.7)	.0007
Myocardial infarction	7.1% (5.2,9.6)	11.3% (6.7,18.4)	16.0% (11.4,22.1)	10.2% (6.45,15.7)	5.4% (2.1,13.1)	14.6% (6.9,28.4)	11.3% (6.8,18.1)	.0216
Heart failure	7.7% (5.7,10.3)	13.9% (8.7,21.4)	12.7% (8.6,18.3)	12.0% (7.9,17.8)	14.9% (8.5,24.7)	17.1% (8.5,31.3)	16.1% (10.7,23.6)	.0457
Stroke or TIA	7.3% (5.4,9.9)	11.3% (6.7,18.4)	10.5% (6.8,15.8)	6.6% (3.7,11.4)	4.0% (1.4,11.2)	9.8% (3.9,22.5)	12.1% (7.5,19.0)	.2651
Atrial fibrillation	7.1% (5.2,9.6)	7.8% (4.2,14.2)	11.0% (7.3,16.4)	7.8% (4.6,12.9)	4.0% (1.4,11.2)	17.1% (8.5,31.3)	7.3% (3.9,13.2)	.1971
Renal failure	3.3% (2.0,5.2)	2.6% (0.9,7.4)	7.2% (4.3,12.0)	4.8% (2.5,9.2)	6.7% (2.9,14.7)	4.9% (1.3,16.1)	11.3% (6.8,18.1)	.0166
Chronic lung disease	30.6% (26.8,34.7)	41.7% (33.1,50.9)	32.2% (25.8,39.4)	33.7% (27.0,41.2)	29.3% (20.2,40.4)	46.3% (32.1,61.2)	27.6% (20.5,36.1)	.1032
Cancer	9.1% (6.9,11.9)	13.9% (8.7,21.4)	14.4% (10.0,20.2)	5.4% (2.9,10.0)	9.3% (4.6,18.0)	2.4% (0.4,12.6)	7.3% (3.9,13.3)	.0413
PTSD	12.5% (9.9,15.6)	8.8% (4.8,15.4)	8.9% (5.5,13.9)	9.6% (6.0,15.1)	8.0% (3.7,16.4)	12.2% (5.3,25.5)	10.5% (6.2,17.1)	.7244
Depression	42.1% (37.9,46.4)	43.0% (34.3,52.1)	33.9% (27.4,41.1)	28.3% (22.0,35.6)	34.7% (24.9,45.9)	17.1% (8.5,31.3)	32.3% (24.7,40.9)	.0016
Dementia	1.3% (0.6,2.7)	4.4% (1.9,9.9)	3.3% (1.5,7.1)	0.6% (0.1,3.3)	1.3% (0.2,7.2)	0.0%	0.8% (0.1,4.4)	.2238

** 95% CI is simultaneous 95% confidence interval after Bonferroni adjustment.

Chronic lung disease included chronic obstructive pulmonary disease, asthma and interstitial lung disease, PTSD – post traumatic stress disorder, TIA – transient ischemic attack.

Table E8. Distribution of primary outcome by patient cluster

Variable/ cluster	mild	PLMS	NREM & poor sleep	REM & hypoxia	hypopnea & hypoxia	arousal & poor sleep	combined severe	Total
Valid N*/ total N	518/533	115/119	181/186	166/168	75/75	41/42	124/124	1222/1247
ACS	26	14	11	11	4	3	13	82
TIA	7	2	2	2	2	1	2	18
Stroke	6	3	4	2	1	0	3	19
Death	47	23	32	22	14	11	21	169
Composite outcome†	82	40	44	36	21	14	34	271

ACS – acute coronary syndrome, TIA – transient ischemic attack.
* Valid N – number of patients with outcome ascertained (i.e. without missing outcome data).
†Composite outcome includes incident stroke, transient ischemic attack, acute coronary syndrome (myocardial infarction, unstable angina, emergency revascularization) or death.

Table E9. Comparison of adjusted Cox proportional hazards models for primary outcome using Framingham risk score (FRS) and Charlson comorbidity index (CCI) (n = 1036*)

Variables	Cluster, CPAP use and Framingham risk score			Cluster, CPAP use and Comorbidity category		
Cluster label	**Hazard Ratio**	**95% CI**	**p-value**	**Hazard Ratio**	**95% CI**	**p-value**
mild	Ref	--		--	--	
PLMS	2.02	1.32, 3.08		2.14	1.46, 3,15	
NREM & poor sleep	1.28	0.85, 1.94		1.59	1.10, 2.31	
REM & hypoxia	1.37	0.89, 2.11	.0265	1.37	0.92,2.04	.0021
hypopnea & hypoxia	1.74	1.02, 2.99		1.69	1.02, 2.81	
arousal & poor sleep	1.79	0.97, 3.29		2.11	1.19, 3.72	
combined severe	1.69	1.09, 2.62		1.76	1.18, 2.65	
Comorbidity						
CCI = 0	--	--		Ref	--	<.0001
CCI = 1, 2	--	--		1.57	1.12, 2.22	
CCI ≥ 3	--	--		3.25	2.31, 4.56	
CPAP use						
Not regular	Ref	--	.0021	Ref	--	.0036
Regular	0.62	0.46, 0.84		0.66	0.50, 0.87	
Framingham risk score (change per 10 points)	1.28	1.19, 1.37	<.0001	--	--	

* subjects without any component of the Framingham risk score excluded

Table E10. Comparison of the Cox proportional hazards models for primary outcome using Framingham risk score (FRS), CPAP use and cluster membership that are unadjusted and adjusted for home oxygen use (n = 1036*)

Variables	Cluster, CPAP use and Framingham risk score			Cluster, CPAP use, Framingham risk score and home oxygen use		
Cluster label	**Hazard Ratio**	**95% CI**	**p-value**	**Hazard Ratio**	**95% CI**	**p-value**
mild	Ref	--		--	--	
PLMS	2.02	1.32, 3.08		1.89	1.24, 2.89	
NREM & poor sleep	1.28	0.85, 1.94		1.17	0.77, 1.78	
REM & hypoxia	1.37	0.89, 2.11	.0265	1.28	0.83, 1.97	.0288
hypopnea & hypoxia	1.74	1.02, 2.99		1.70	0.99, 2.92	
arousal & poor sleep	1.79	0.97, 3.29		1.79	0.98, 3.30	
combined severe	1.69	1.09, 2.62		1.74	1.12, 2.71	
Home oxygen use						
None	--	--		Ref	--	<.0001
Present	--	--		4.10	2.90, 5.79	
CPAP use						
Not regular	Ref	--	.0021	Ref	--	.0004
Regular	0.62	0.46, 0.84		0.58	0.43, 0.78	
Framingham risk score (change per 10 points)	1.28	1.19, 1.37	<.0001	1.26	1.18, 1.36	<.0001

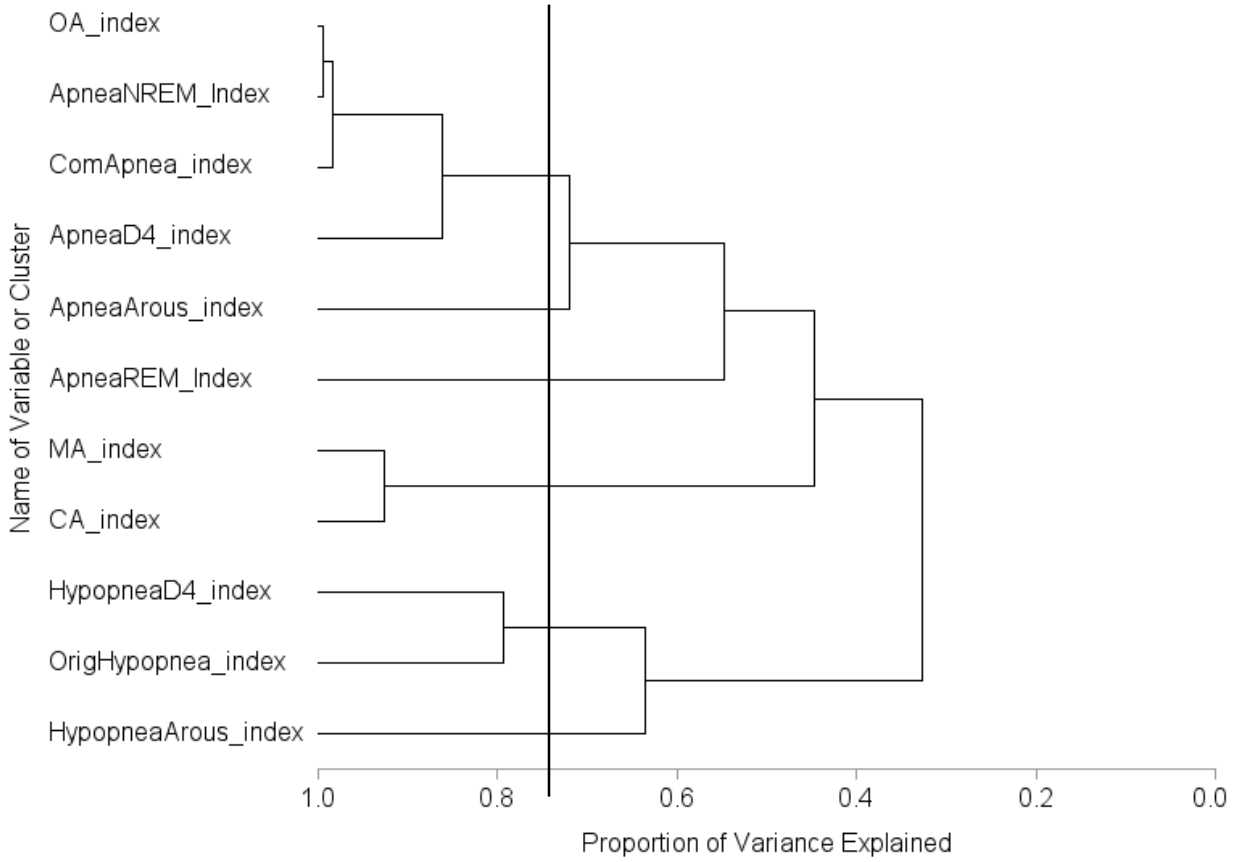
* subjects without any component of the Framingham risk score excluded

Table E11. Comparison of patient characteristics between the analytic sample (n=1247) and excluded patients (n=794).

Variable Sample /Statistic	Analytic sample			Excluded patients			T-test or X^2
	N	Mean or proportion	St. Dev.	N	Mean or proportion	St. Dev.	P-value
Age	1247	58.3	11.7	776	57.3	11.0	0.061
Male	1247	94.9%	--	792	94.1%	--	0.437
White	1147	85.3%	--	747	80.6%	--	0.006
Black		12.2%	--		17.4%	--	
Other race		2.5%	--		2.0%	--	
AHI (#/hour)*	1247	25.0	29.7	304	22.0	27.1	0.307
BMI (kg/m^2)	1175	34.6	7.3	731	35.0	7.8	0.285
Framingham risk score	1042	27.5	17.3	642	26.9	16.8	0.487
CCI*	1247	1.7	2.0	794	1.8	2.89	0.221
Primary outcome	1222	22.2%	--	774	21.3%	--	0.637

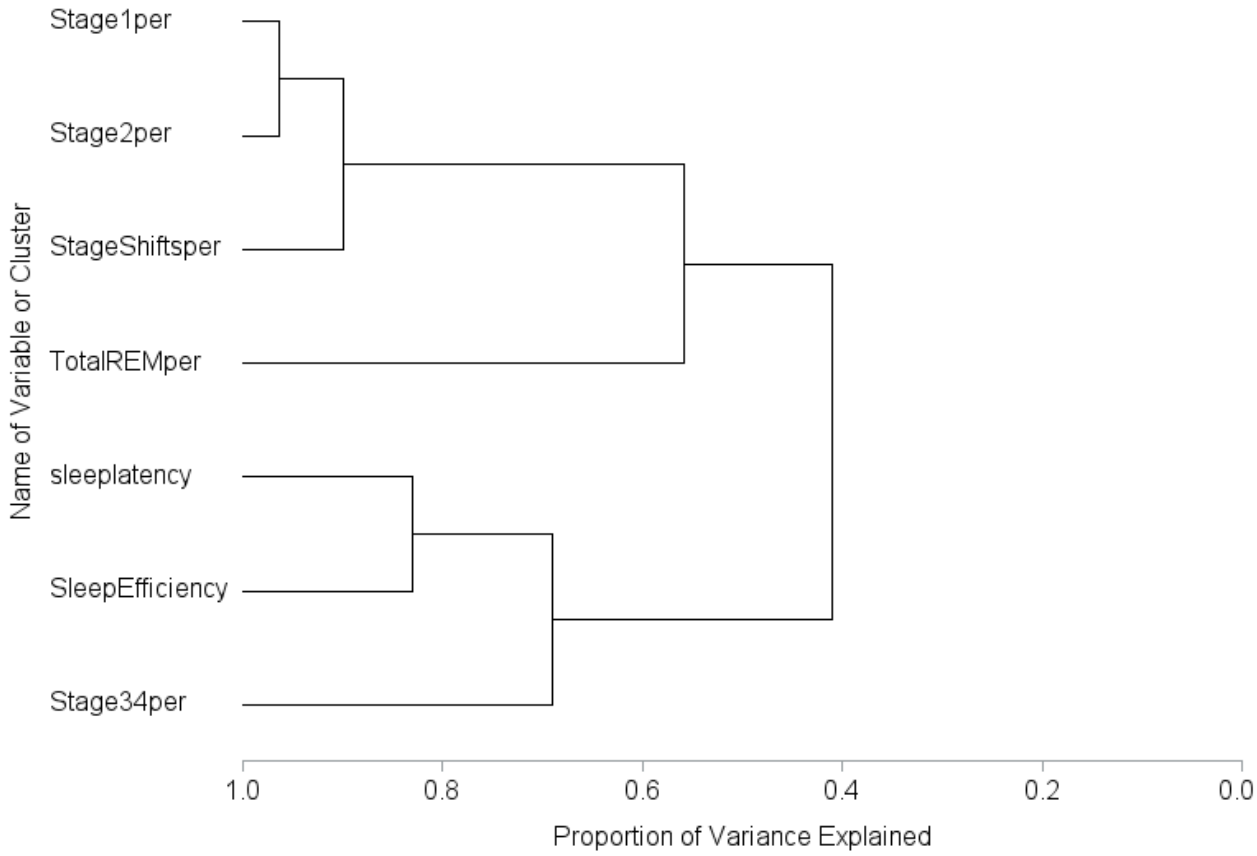
AHI – apnea hypopnea index
CCI – Charlson comorbidity index
OSA severity: Mild/none, AHI<15; moderate, 15≤AHI<30; severe, AHI≥30
Analytic sample (n=1247), excluded patients (n=795).

Figure E1a. Dendrogram of variable reduction analysis for the breathing disturbance variables (vertical line represents feature membership based on >75% of variance explained as an example) in the analytic sample (n=1248).



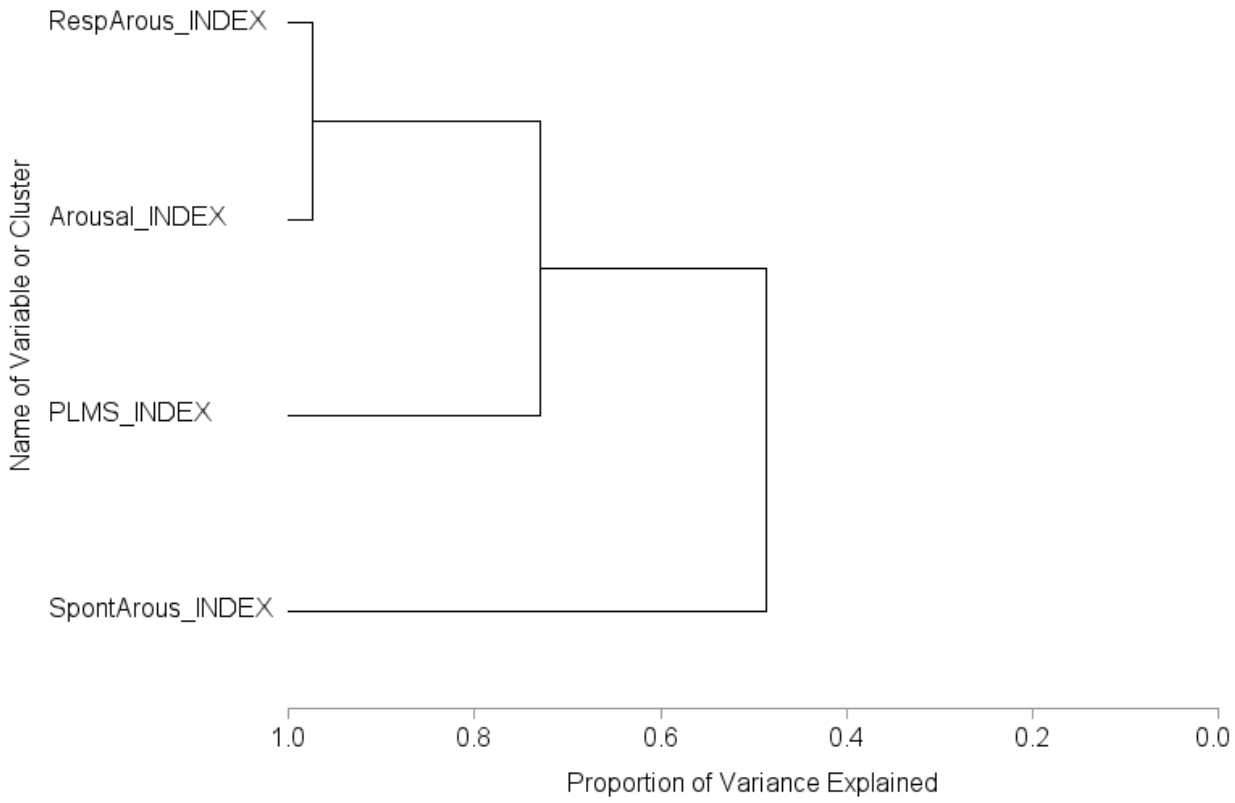
Apnea D4 – apnea with 4% desaturation but without arousal, ComApnea – Combined Apnea (apnea with 4% desaturation and arousal), ApneaArous – apnea with arousal and without desaturation. Hypopnea D4 and Hypopnea Arousal are defined in same manner as apneas, Original Hypopnea – hypopnea with 4% desaturation with or without arousal. OA, CA,MA – obstructive, central and mixed apneas respectively. REM – rapid eye movement, NREM – non-rapid eye movement.

Figure E1b. Dendrogram of variable reduction analysis for the sleep architecture variables in the analytic sample (n=1248).



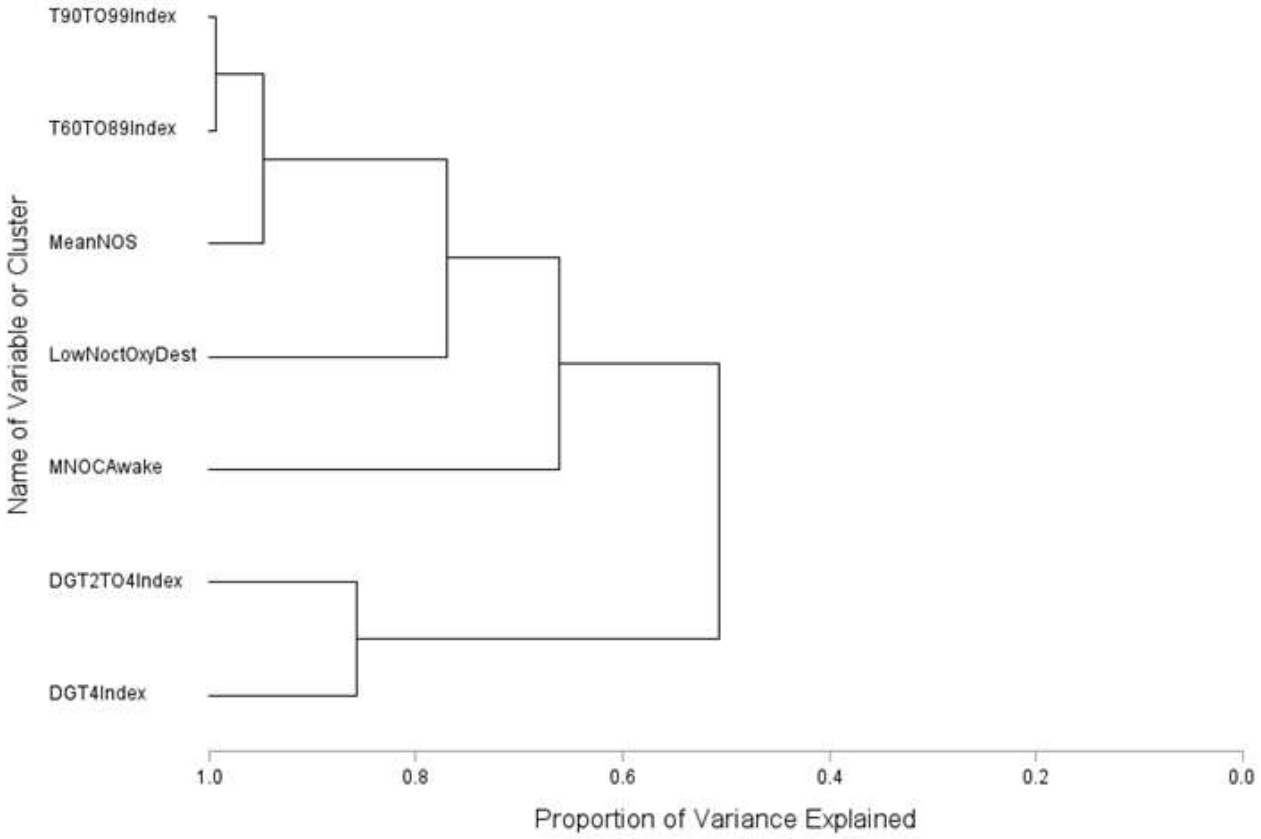
Stage1per – % of total sleep time (TST) in stage 1 sleep, Stage2per – % TST in stage 2 sleep, Stage134per – % TST in stage 3 and 4 sleep, StageShiftsper – index of stage shifts, TotalREMper - % TST in REM sleep.

Figure E1c. Dendrogram of variable reduction analysis for the autonomic dysfunction variables in the analytic sample (n=1248).



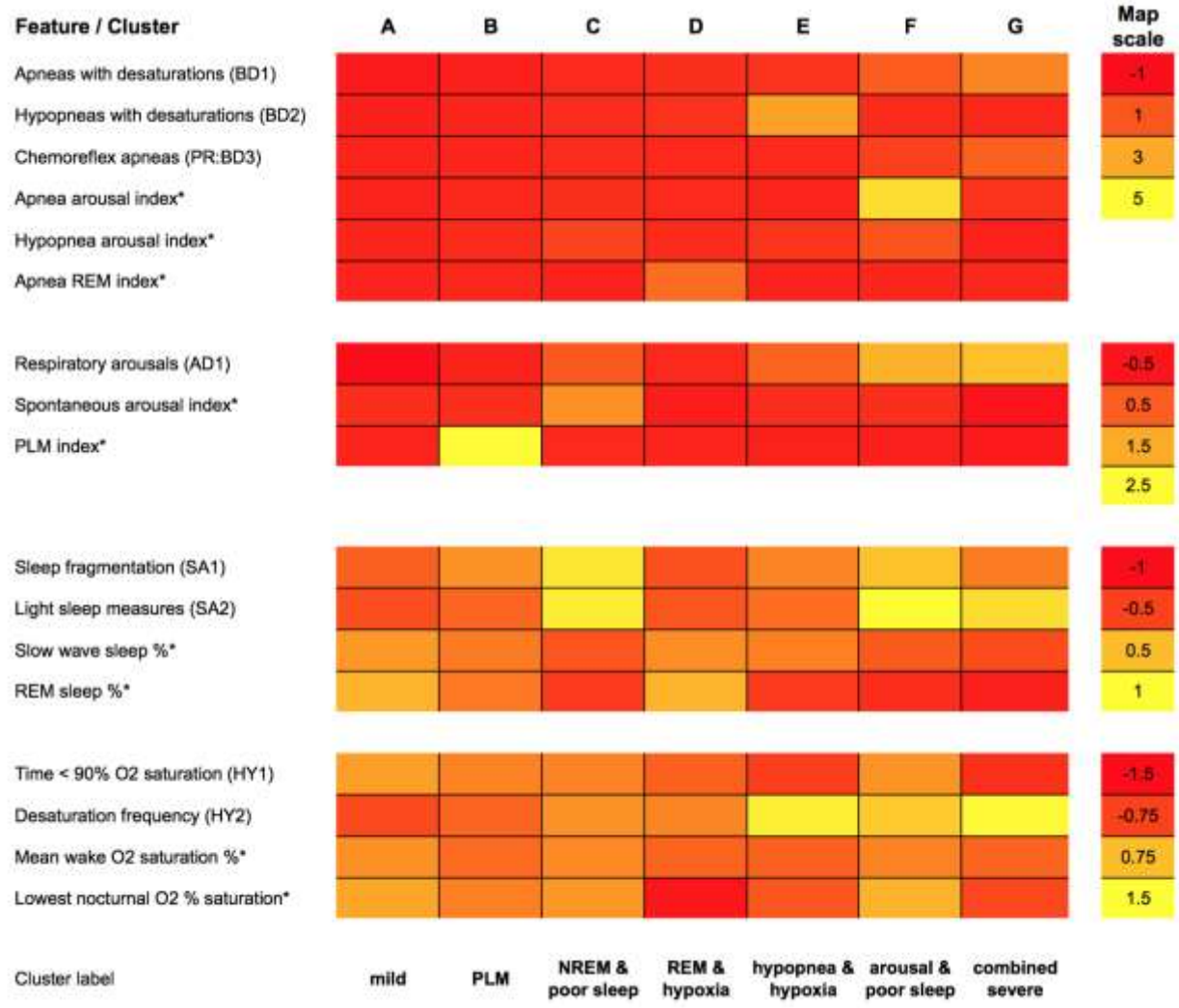
Arousal_INDEX – total arousal index, PLMS_INDEX – periodic leg movement of sleep arousal index, RespArous_INDEX – respiratory arousal index, SpontArous_INDEX – spontaneous arousal index

Figure E1d. Dendrogram of variable reduction analysis for the hypoxia variables in the analytic sample (n=1248).



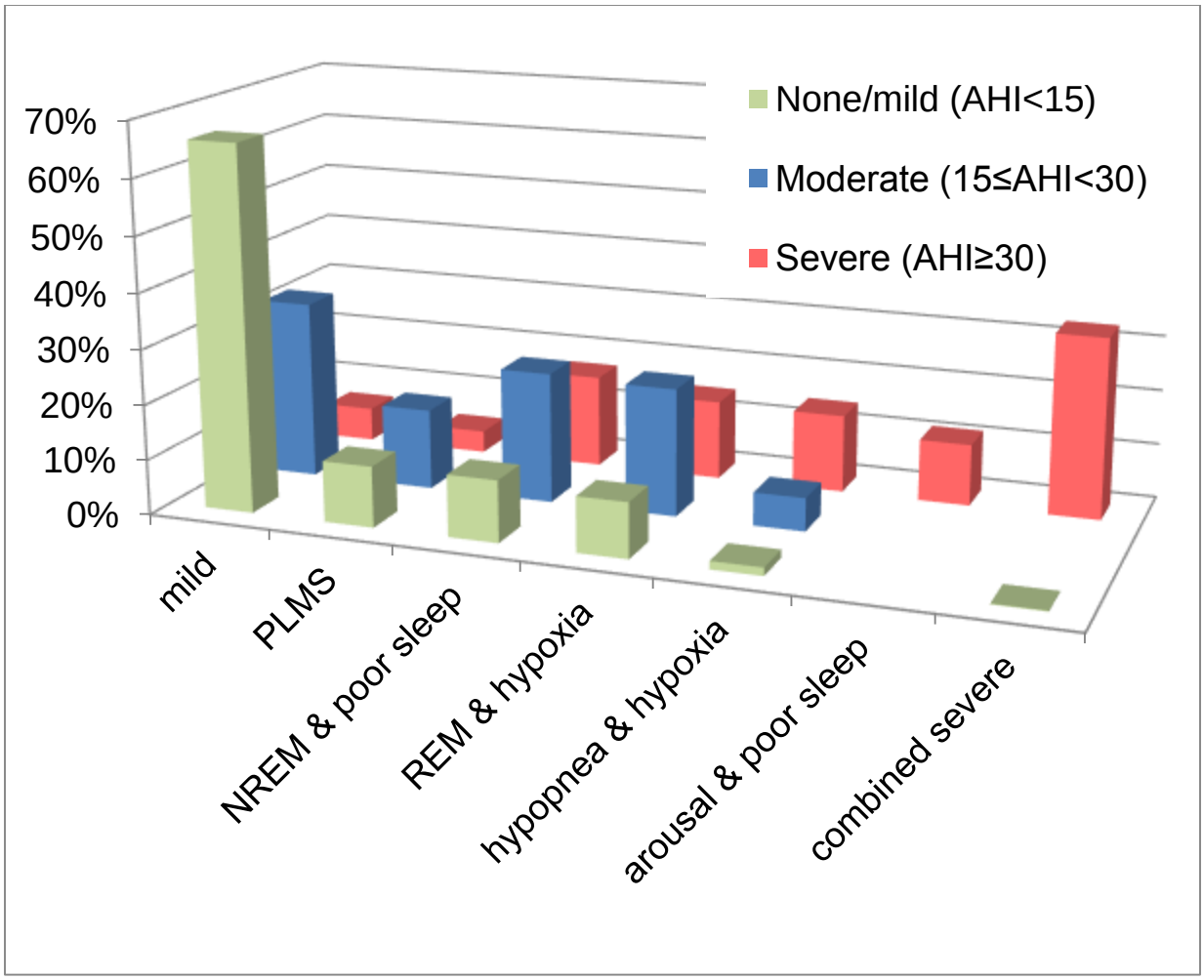
DGT2TO4Index – oxygen desaturation index of 2 to 4%, DGT4Index – oxygen desaturation index of > 4%, LowNoctOxyDest – lowest nocturnal oxygen saturation, MeanNOCAwake – mean nocturnal oxygen saturation while awake, MeanNOS – mean nocturnal oxygen saturation,

Figure E2. Heat map of standardized feature principal component scores among the 7 patient clusters (A – G) for polysomnographic domains (top to bottom: breathing disturbance, autonomic dysfunction, sleep architecture disturbance, hypoxemia)



* Variable values standardized for comparison with principal component scores for each feature
BD1 – Principal component of obstructive apnea, apnea D4, combined apnea, apnea NREM indices
BD2 – Principal component of Hypopnea D4, original hypopnea indices
BD3 – Principal component of Mixed apnea and central apnea indices
AD1 – Principal component of respiratory arousal and arousal indices
SA1 – Principal component of sleep latency and sleep efficiency
SA2 – Principal component of Stage 1, 2, Stage shifts %
HY1 – Principal component of Mean nocturnal O_2 saturation, T90% index
HY2 – Principal component of DGT2to4% and DGT<4% indices

Figure E3. Prevalence of cluster membership within each conventional AHI-based sleep apnea severity category (none/mild, moderate and severe).



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