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SCIENTIFIC INVESTIGATIONS

Cluster-derived obstructive sleep apnea phenotypes and outcomes at 5-year follow-up

María Guadalupe Silveira, MD[1,2]; Gabriel Sampol, MD, PhD[2,3,4,5]; Miriam Mota-Foix, MSc[6]; Jaume Ferrer, MD, PhD[2,4,5]; Patricia Lloberes, MD, PhD[3,4,5]

[1]Pneumology Department, Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Spain; [2]Medicine Department, Universitat Autònoma de Barcelona, Barcelona, Spain; [3]Multidisciplinary Sleep Unit, Pneumology Department, Vall d'Hebron University Hospital, Barcelona, Spain; [4]Pneumology Department, Vall d'Hebron University Hospital, Barcelona, Spain; [5]Centro de Investigación Biomédica en Red Enfermedades Respiratorias (CIBERES), Instituto de la Salud Carlos III (ISCIIII), Madrid, Spain; [6]Statistics and Bioinformatics Unit, Vall d'Hebron Research Institute, Barcelona, Spain

Study Objectives: Obstructive sleep apnea (OSA) is a heterogeneous, complex disease. We aimed to identify OSA phenotypes through cluster analysis and to perform a long-term follow-up to validate the phenotypes.

Methods: We applied a partitioning around medioids technique in a cohort of 1,217 participants recently diagnosed with OSA. We performed a 5-year follow-up analyzing the incidence of comorbidities, chronic medication, hospital admissions, mortality, and the influence of continuous positive airway pressure treatment on mortality risk.

Results: We identified three phenotypes: two predominantly male clusters, one composed of middle-aged participants with overweight, moderate OSA, and cardiovascular risk factors and the other consisting of older, obese participants with severe OSA, cardiovascular risk factors, ischemic heart disease (18.4%), and atrial fibrillation (9.7%). The third cluster was composed of 77% female participants with moderate OSA; cardiovascular risk factors; the highest prevalence of depression (15.7%); and high prescription of antidepressants (55.1%), anxiolytics (40.0%), hypnotics, sedatives (11.1%), nonsteroidal anti-inflammatory drugs (67.9%), and weak opioids (15.1%). The baseline characteristics of each cluster maintained the same trend over time regarding the incidence of new comorbidities, medication intake, hospitalization rates, and reasons for admission. The absence of continuous positive airway pressure treatment was associated with a significantly higher risk of all-cause mortality (hazard ratio 5.84, confidence interval 2.9–11.8), especially in the older men (hazard ratio 7.7, confidence interval 4.06–14.63) and predominantly female clusters (hazard ratio 2.79, confidence interval 1.34–5.79).

Conclusions: We identified three phenotypes with relevant clinical and prognostic implications in order to improve personalized strategies in OSA management.

Keywords: OSA, phenotypes, comorbidities, CPAP

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Obstructive sleep apnea is a heterogeneous disease associated with multiple comorbidities. Many studies have been conducted to identify specific obstructive sleep apnea phenotypes through cluster analyses, but most of these are cross-sectional and their associations with clinical outcomes are still controversial.

Study Impact: We performed a new cluster analysis using extensive information on sleep studies, comorbidities, and chronic medication, carried out a long-term follow-up, and analyzed the impact of continuous positive airway pressure treatment. In this way, we were able to identify three phenotypes, validate them over time, and associate them with relevant clinical outcomes, which will help improve personalized strategies in obstructive sleep apnea management.

INTRODUCTION

Obstructive sleep apnea (OSA) is a multifactorial and heterogeneous disease.[1] In the last decade, to improve OSA management through a personalized approach, cluster analysis, a statistical method that allows classifying subjects from a large number of variables into groups that differ from each other, has been applied in different OSA cohorts.[2]

The specific groups identified depend on the data set used by the investigators. In OSA, most studies have used symptomatology, comorbidities, and polysomnographic data. As a result, a number of distinctive OSA phenotypes have been described that are difficult to compare across studies. Moreover, the identification of similar patient subgroups related to relevant clinical outcomes from these studies is controversial: OSA symptom subtypes have been proposed to be clinically relevant, but discordant results regarding their relationship to cardiovascular disease have been described.[3–6]

On the other hand, cluster analyses are cross-sectional; thus, when an association between clusters and clinical outcomes is found, this association is only valid at a specific point in time, not providing information on the long-term behavior or prognostic value. Only a few studies have performed a follow-up of phenotypes over time regarding cardiovascular risk and continuous positive airway pressure (CPAP) treatment outcomes.[6–10] Analyzing specific phenotypes' evolution and response to treatment

over time could help to ascertain their clinical implications and improve OSA risk stratification for customized therapies.

We hypothesized that we would be able to identify different OSA phenotypes based on a large number of clinical variables and OSA severity measures, that these phenotypes would maintain their defining characteristics in the long term, and that CPAP treatment would impact outcomes differently in each group.

Our study had two main objectives. The first was to perform a new cluster analysis aimed at identifying relevant OSA phenotypes using clinical, anthropometric, comorbidities, and polysomnographic data and, furthermore, comprehensive medicine prescription information, adding another dimension to the spectrum of participant features used until now. The second was to validate the identified clusters performing a 5-year follow-up, analyzing the incidence of comorbidities, prescription of chronic medication, hospital admissions, and mortality and to assess the influence of CPAP treatment on mortality risk.

METHODS

Design, setting, and study population

We performed a retrospective study on a cohort of 1,217 consecutive adult patients newly diagnosed with OSA during 2009 and 2010 in the Sleep Unit of a tertiary hospital in Barcelona, Spain (with a reference area of 439,514 inhabitants). Follow-up was performed till December 2015. The study was approved by the hospital's ethics committee [PR(AG)267/2014]. Since all data were anonymized, individual patient consent was not required.

Sleep studies

Patients were diagnosed using home-based respiratory polygraphy (Somnea Compumedics, Abbotsford, Victoria, Australia) or sleep laboratory-based polysomnography (Profusion E Series, Compumedics, Abbotsford, Victoria, Australia). Sleep studies were evaluated according to the 2007 American Academy of Sleep Medicine standard criteria[11] with the alternative definition for hypopnea: a 50% or more reduction in nasal pressure signal for ≥ 10 seconds associated with ≥ 3% desaturation or an arousal. OSA was defined as an apnea-hypopnea index (AHI) equal to or higher than 5 events/h.

Clinical variables and treatment data

Comorbidities and chronic medicine prescriptions were obtained from the Agency for Health Quality and Assessment of Catalonia. All the conditions present from the date of the diagnostic sleep test till the end of follow-up were registered and coded at each contact with the Catalan Public Health Service (in primary care, hospital, or nursing home), according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision.[12] Drugs were registered in the electronic medical records every time a physician had prescribed or renewed a medication since the year 2008 and were classified according to the Anatomical, Therapeutic, Chemical (ATC) classification system.[13]

Baseline information on anthropometric data and assessment of daytime somnolence by the Epworth Sleepiness Scale (ESS) were collected from the hospital's medical records.

We also obtained from the Agency for Health Quality and Assessment of Catalonia information on hospital admissions, medical procedures, and reported deaths during follow-up. Causes of death were obtained from the hospital's medical records. Causes of deaths of participants dying outside the hospital setting were not available and were registered as "unknown."

CPAP treatment was prescribed according to the Spanish Society of Pulmonology and Thoracic Surgery's guidelines on the diagnosis and treatment of OSA. CPAP is prescribed to patients with mild or moderate OSA with excessive daytime sleepiness or cardiovascular disease, depending on the physician's criteria, and to patients with severe OSA, regardless of symptomatology.[14] Data on CPAP prescription and discontinuation were provided by the official Catalan Health System's CPAP suppliers. In Catalonia, CPAP treatment is suspended during follow-up if patients do not comply with a mean use of CPAP of at least 3 hours a night. We defined "CPAP users" as those who were receiving active treatment at the end of follow-up. "No CPAP" was considered when CPAP was not prescribed or was prescribed but later discontinued.

Baseline dataset for cluster analysis

The final dataset of variables used for clustering included baseline anthropometric data (sex, age, and body mass index [BMI]), polysomnography/respiratory polygraphy data (AHI; baseline, mean, and minimum oxygen saturation; percentage of time with oxygen saturation below 90% [CT90%]; oxygen desaturation index > 3%; and oxygen desaturation index > 4%), ESS, comorbidities, and chronic medicine consumption.

Follow-up outcomes

We analyzed the incidence of new comorbidities, number and cause of hospital admissions, mortality, and cause of death during follow-up in each cluster. We also assessed chronic medicine prescription at the end of follow-up. In addition, the same analyses were performed to compare within each cluster CPAP users vs No CPAP users.

Statistical and cluster analysis

Statistical analysis was carried out in the Statistics and Bioinformatics Unit of the Vall d'Hebron Hospital Research Institute.

For variables with missing data, the values were imputed using the multivariate imputation by chained equations method. To increase the robustness of the analyses, numerical variables were scaled. Given the high number of variables, we proceeded to the reduction of the dimension by creating a reduced number of new variables (components) from the linear combinations of the original variables. The Euclidean distance was calculated, specifically for quantitative variables. Once the distance matrix was obtained, we proceeded to estimate the groups from the partition around medoids method. For choosing the number of

optimal groups to use for cluster analysis we used a silhouette width method.

After the selection of clusters, a comparison between groups was performed to detect variables that define groups. For categorical variables, frequencies (total and percentage) and the 95% confidence interval were calculated. For continuous variables, mean and standard deviation, the 95% confidence interval for the mean, and the median and the interquartile range were calculated. Comparison tests between groups were carried out; for quantitative variables, an ANOVA or a Kruskall-Wallis test was performed. For categorical variables, a chi-square test or Fisher's exact test was performed. Since many comparisons were made in the follow-up analysis, in order to adjust the *P* values we used the false discovery rates method,[15] which corrects the *P* value by correcting the probability of obtaining a false positive. For all analyses, a *P* value of less than .05 was considered statistically significant.

Cox proportional hazards models and Kaplan-Meier survival analysis were used to evaluate associations between the different clusters and all-cause mortality during follow-up, adjusting for CPAP treatment.

Statistical analysis was performed using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Further methodological details are found in the supplemental material.

RESULTS

Cohort's characteristics

During 2014, 1,217 participants were diagnosed with OSA. Missing data were 3.45% regarding anthropometrics, polygraphic parameters, and ESS. The diagnostic method was full polysomnography in 32.8% of the participants and respiratory polygraphy in 67.2%. The sample consisted predominantly of middle-aged, obese male participants with moderate or severe OSA. Mean age (standard deviation) was 58.1 (13) years, 71.4% were men, mean BMI was 30.7 (5.4) kg/m^2, and mean AHI was 32.4 events/h (23.3). Only 25.5% of participants showed an ESS higher than 10 [mean 7.2 (4.4)]. The total cohort general characteristics and the results of the sleep studies are summarized in **Table 1**. Information on the prevalence of comorbidities and medicine prescription in the whole cohort is detailed in **Table S1** in the supplemental material. Information on chronic medication showed a much higher prescription of antidepressants, anxiolytics, and hypnotics and sedatives (26.13%, 19.06%, and 4.44%, respectively) than one that would correspond to the reported diagnoses of depression (9.04%) and insomnia (0.74%). In addition, we found high rates of chronic prescriptions of nonsteroidal anti-inflammatory drugs (36.89%) and weak opioids (7.64%), suggesting a high prevalence of chronic pain.

Cluster analysis

All conditions with a number of participants lower than 50 were considered "Other." Considering a minimum of 2 and a maximum of 10 for the partition around medoids algorithm, the best group-value relationship corresponded to 3 groups. The general characteristics and the results of the sleep studies in the 3 clusters are depicted in **Table 2**. In order to visualize the data set, a heat map was obtained, taking into account variables with a *P* value < .05 (**Figure S1** in the supplemental material). This graph represents the scaled values where intensities were color-coded to highlight possible patterns between groups.

Cluster 1 ("healthy, middle-aged men with moderate OSA"): Included 553 participants (45.4%), predominantly men (88.6%), mean age 51.1(12.4) years, with overweight [BMI 29.4 (5) kg/m^2], moderate OSA [mean AHI 27.8 events/h (20)], without sleepiness [ESS 7.5 (4.3)], and slight nighttime hypoxemia [CT90% 9.7 (14.6)]. This cluster showed the lowest prevalence of comorbidities and chronic medications, with a moderate prevalence of hypertension (20.4%) and dyslipidemia (27.7%).

Cluster 2 ("older men with cardiovascular risk factors and disease and severe OSA"): Included 359 patients (29.5%), mostly men (86.1%), mean age 63.4 (11) years, obese [BMI 32.7 (5.6) kg/m^2)], with severe OSA [mean AHI 45.8 events/h (26.9)], without sleepiness [ESS 8 (4.6)], and greater nocturnal hypoxemia [CT90% 28.4 (29.3)]. This cluster showed the highest prevalence of cardiovascular risk factors, such as hypertension (73%), dyslipidemia (76.3%), type 2 diabetes (48.5%), and a significantly higher prevalence of ischemic heart disease (18.4%) and atrial fibrillation (9.7%), as well as medication intake related to cardiovascular disease, compared with the other clusters.

Table 1—Cohort general characteristics and sleep studies data (n = 1,217).

Variables	
Age, y	58.1 (13) [57.3;58.8]
Sex	
Female	348 (28.6%)
Male	869 (71.4%)
BMI, kg/m^2	30.7 (5.4) [30.4;31]
ESS	7.2 (4.4) [6.9;7.4]
AHI, events/h	32.4 (23.3) [31.1;33.7]
OSA severity	
Mild	336 (27.6%)
Moderate	354 (29.1%)
Severe	527 (43.3%)
Daytime SaO_2%	95.8 (4.2) [95.6;96.1]
Mean SaO_2%	92.9 (4.3) [92.7;93.2]
Minimum SaO_2%	61.9 (29.6) [60.2;63.6]
CT90%	15.5 (22.3) [14.2;16.7]
ODI 3%	33.4 (25.6) [32;34.9]
ODI 4%	28.3 (24.8) [26.9;29.7]

Data are shown as mean (standard deviation) and confidence interval [CI], except sex and OSA severity, which are expressed as frequency (percentage). AHI = apnea-hypopnea index; BMI = body mass index, CT90 = time percentage with SaO_2 < 90%, ESS = Epworth Sleepiness Scale, ODI = oxygen desaturation index, OSA = obstructive sleep apnea, SaO_2 = oxygen saturation.

Table 2—Characteristics of the different clusters.

	Cluster 1	Cluster 2	Cluster 3	*P*
Participants	553 (45.4)	359 (29.5)	305 (25)	
Anthropometric and polygraphic variables				
Age, y	51.1 (12.4) [50; 52.1]	63.4 (11) [62.2; 64.5]	64.5 (9.3) [63.5; 65.6]	< .001
Sex				
Female	63 (11.4%) [8.9; 14.3]	50 (13.9%) [10.5; 17.9]	235 (77%) [71.9; 81.6]	< .001
Male	490 (88.6%) [85.7; 91.1]	309 (86.1%) [82.1; 89.5]	70 (23%) [18.4; 28.1]	
BMI, kg/m^2	29.4 (5) [29; 29.8]	32.7 (5.6) [32.1; 33.2]	30.7 (5.4) [30.1; 31.3]	< .001
ESS	7.5 (4.3) [7.1; 7.8]	8 (4.6) [7.5; 8.5]	5.9 (3.9) [5.4; 6.3]	< .001
AHI, events/h	27.8 (20) [26.1; 29.5]	45.8 (26.9) [43; 48.5]	25.2 (17) [23.3; 27.1]	< .001
OSA severity				
Mild	189 (34.2%) CI[30.2; 38.3]	47 (13.1%) CI[9.8; 17]	100 (32.8%) CI[27.5; 38.4]	< .001
Moderate	166 (30%) CI[26.2; 34]	73 (20.3%) CI[16.3; 24.9]	115 (37.7%) CI[32.2; 43.4]	
Severe	198 (35.8%) CI[31.8; 40]	239 (66.6%) CI[61.4; 71.4]	90 (29.5%) CI[24.4; 35]	
Daytime SaO_2%	96.6 (3.7) [96.3; 96.9]	94.8 (5) [94.3; 95.3]	95.6 (3.5) [95.2; 96]	< .001
Mean SaO_2%	94.1 (2.8) [93.8; 94.3]	90.9 (6) [90.3; 91.6]	93.3 (3.2) [93; 93.7]	< .001
Minimum SaO_2%	69.7 (25) [67.6; 71.8]	50.8 (31) [47.6; 54.1]	60.3 (31.7) [56.7; 63.9]	< .001
CT90%	9.7 (14.6) [8.5; 10.9]	28.4 (29.3) [25.4; 31.5]	10.5 (17.5) [8.5; 12.5]	< .001
ODI 3%	28 (21.4) [26.2; 29.8]	48.9 (29.4) [45.9; 52]	25 (19.2) [22.9; 27.2]	< .001
ODI 4%	23 (20.2) [21.3; 24.7]	43.2 (29.4) [40.2; 46.3]	20.3 (17.7) [18.3; 22.3]	< .001
Comorbidities				
Hypertension	113 (20.4%) [17.1; 24]	262 (73%) [68.1; 77.5]	195 (63.9%) [58.3; 69.3]	< .001
Dyslipidemia	153 (27.7%) [24; 31.6]	274 (76.3%) [71.6; 80.6]	192 (63%) [57.3; 68.4]	< .001
Type 2 diabetes mellitus	23 (4.2%) [2.7; 6.2]	174 (48.5%) [43.2; 53.8]	44 (14.4%) [10.7; 18.9]	< .001
Ischemic heart disease	5 (0.9%) [0.3; 2.1]	66 (18.4%) [14.5; 22.8]	19 (6.2%) [3.8; 9.6]	< .001
Atrial fibrillation	5 (0.9%) [0.3; 2.1]	35 (9.7%) [6.9; 13.3]	15 (4.9%) [2.8; 8]	< .001
COPD	25 (4.5%) [2.9; 6.6]	33 (9.2%) [6.4; 12.7]	24 (7.9%) [5.1; 11.5]	.015
Depressive disorder	28 (5.1%) [3.4; 7.2]	34 (9.5%) [6.6; 13]	48 (15.7%) [11.8; 20.3]	< .001
Solid neoplasm	17 (3.1%) [1.8; 4.9]	23 (6.4%) [4.1; 9.5]	18 (5.9%) [3.5; 9.2]	.039
Other	65 (11.8%) [9.2; 14.7]	124 (34.5%) [29.6; 39.7]	72 (23.6%) [19; 28.8]	< .001
Tobacco use	122 (22.1%) [18.7; 25.8]	77 (21.4%) [17.3; 26.1]	40 (13.1%) [9.5; 17.4]	.004
Medicine prescription				
Beta blockers	7 (1.3%) [0.5; 2.6]	166 (46.2%) [41; 51.5]	22 (7.2%) [4.6; 10.7]	< .001
Calcium blockers	15 (2.7%) [1.5; 4.4]	121 (33.7%) [28.8; 38.9]	57 (18.7%) [14.5; 23.5]	< .001
Angiotensin-converting enzyme inhibitors	79 (14.3%) [11.5; 17.5]	268 (74.7%) [69.8; 79.1]	166 (54.4%) [48.7; 60.1]	< .001
Diuretics	34 (6.1%) [4.3; 8.5]	153 (42.6%) [37.4; 47.9]	96 (31.5%) [26.3; 37]	< .001
Antihypertensives	7 (1.3%) [0.5; 2.6]	39 (10.9%) [7.8; 14.6]	16 (5.2%) [3; 8.4]	< .001
Lipid-lowering agents	62 (11.2%) [8.7; 14.1]	229 (63.8%) [58.6; 68.8]	149 (48.9%) [43.1; 54.6]	< .001
Oral hypoglycemic agents	8 (1.4%) [0.6; 2.8]	142 (39.6%) [34.5; 44.8]	28 (9.2%) [6.2; 13]	< .001
Insulins	4 (0.7%) [0.2; 1.8]	55 (15.3%) [11.8; 19.5]	10 (3.3%) [1.6; 5.9]	< .001
Antiarrhythmics	7 (1.3%) [0.5; 2.6]	24 (6.7%) [4.3; 9.8]	18 (5.9%) [3.5; 9.2]	< .001
Antiplatelets	21 (3.8%) [2.4; 5.7]	162 (45.1%) [39.9; 50.4]	70 (23%) [18.4; 28.1]	< .001
Anticoagulants	10 (1.8%) [0.9; 3.3]	56 (15.6%) [12; 19.8]	18 (5.9%) [3.5; 9.2]	< .001
Vasodilators for cardiac diseases	0 (0%) [0; 0.7]	29 (8.1%) [5.5; 11.4]	19 (6.2%) [3.8; 9.6]	< .001
Bronchodilators	54 (9.8%) [7.4; 12.5]	101 (28.1%) [23.5; 33.1]	67 (22%) [17.4; 27]	< .001
NSAIDs	115 (20.8%) [17.5; 24.4]	127 (35.4%) [30.4; 40.6]	207 (67.9%) [62.3; 73.1]	< .001

(continued on following page)

Table 2—Characteristics of the different clusters. (*Continued*)

	Cluster 1	Cluster 2	Cluster 3	*P*
Weak opioids	11 (2%) [1; 3.5]	36 (10%) [7.1; 13.6]	46 (15.1%) [11.3; 19.6]	< .001
Anxiolytics	48 (8.7%) [6.5; 11.3]	62 (17.3%) [13.5; 21.6]	122 (40%) [34.5; 45.7]	< .001
Antidepressants	77 (13.9%) [11.1; 17.1]	73 (20.3%) [16.3; 24.9]	168 (55.1%) [49.3; 60.8]	< .001
Hypnotics and sedatives	8 (1.4%) [0.6; 2.8]	12 (3.3%) [1.7; 5.8]	34 (11.1%) [7.8; 15.2]	< .001

Only comorbidities and medications that are statistically significantly different are shown in the table. Data are shown as frequency (percentage) and [95% confidence interval] for categorical variables and as mean (standard deviation) and [95% confidence interval] for continuous variables. AHI = apnea-hypopnea index, BMI = body mass index, COPD = chronic obstructive pulmonary disease, CT90 = time percentage with SaO_2 < 90%, ESS = Epworth Sleepiness Scale, NSAIDs = nonsteroidal anti-inflammatory drugs, ODI = oxygen desaturation index, SaO_2 = oxygen saturation.

Cluster 3 ("older women with cardiovascular risk factors, depression, and moderate OSA"): This cluster was composed of 305 participants (25%), with a predominance of women (77%), mean age 64.5 (9.3) years, obese [BMI 30.7 (5.4) kg/m^2], moderate OSA [mean AHI 25.2 events/h (17)], without sleepiness [ESS 5.9 (3.9)], and slight nighttime desaturation [CT90% 10.5 (17.5)]. This group also presented a high prevalence of hypertension (63.9%) and dyslipidemia 63%), the highest prevalence of depression (15.7%), and a high consumption of antidepressants (55.1%), anxiolytics (40%), hypnotics and sedatives (11.1%), nonsteroidal anti-inflammatory drugs (67.9%), and weak opioids (15.1%).

Tobacco use was similar in clusters 1 and 2. Chronic obstructive pulmonary disease and the use of bronchodilators were similar in clusters 2 and 3, although smoking was much lower in number 3. Solid neoplasms were more frequent in clusters 2 and 3, and cluster 2 had a higher frequency of "other" diseases.

Evolution over time

The mean follow-up was 5.8 (0.8) years. The incidence of new comorbidities per person in the cohort was 1 (1.1). Half of the participants (50.5%) required hospitalization at some point, and the mortality rate was 6.1% (74 participants). The cause of death was unknown in 29.7% of participants, and cancer was the most frequent known cause (31.1%).

In cluster 1 the incidence of new comorbidities per person was significantly lower [0.8 (1.1)] compared to clusters 2 [1.2 (1.2)] and 3 [1.1 (1.1)] (**Table 3**). Only the incidence of hypertension (13.4%) and dyslipidemia (20.3%) was similar to the other groups.

Clusters 2 and 3 presented similar incidences of cardiovascular risk factors: hypertension (15.3% and 13.1%, respectively), type 2 diabetes (14.5% and 16.4%), and dyslipidemia (18.9% and 21.6%) as well as cerebrovascular disease (7.5% and 5.2%). Compared with cluster 3, cluster 2 showed a significantly higher incidence of heart failure (24.8% vs 9.5%), atrial fibrillation

Table 3—Incidence of comorbidities in each cluster during follow-up.

	Cluster 1	Cluster 2	Cluster 3	*P*
New comorbidities per participant	0.8 (1.1) [0.7; 0.9]	1.2 (1.2) [1.1; 1.3]	1.1 (1.1) [1; 1.2]	< .001*
Comorbidities				
Hypertension	74 (13.4%) [10.7; 16.5]	55 (15.3%) [11.8; 19.5]	40 (13.1%) [9.5; 17.4]	.68
Dyslipidemia	112 (20.3%) [17; 23.8]	68 (18.9%) [15; 23.4]	66 (21.6%) [17.1; 26.7]	.69
Type 2 diabetes mellitus	47 (8.5%) [6.3; 11.1]	52 (14.5%) [11; 18.6]	50 (16.4%) [12.4; 21]	< .001*
Heart failure	11 (2%) [1; 3.5]	89 (24.8%) [20.4; 29.6]	29 (9.5%) [6.5; 13.4]	< .001*
Atrial fibrillation	20 (3.6%) [2.2; 5.5]	57 (15.9%) [12.3; 20.1]	29 (9.5%) [6.5; 13.4]	< .001*
Ischemic heart disease	11 (2%) [1; 3.5]	52 (14.5%) [11; 18.6]	15 (4.9%) [2.8; 8]	< .001*
Cerebrovascular disease	11 (2%) [1; 3.5]	27 (7.5%) [5; 10.8]	16 (5.2%) [3; 8.4]	< .001*
Chronic kidney disease	17 (3.1%) [1.8; 4.9]	78 (21.7%) [17.6; 26.4]	32 (10.5%) [7.3; 14.5]	< .001*
Chronic obstructive pulmonary disease	21 (3.8%) [2.4; 5.7]	35 (9.7%) [6.9; 13.3]	15 (4.9%) [2.8; 8]	< .001*
Solid neoplasms	24 (4.3%) [2.8; 6.4]	30 (8.4%) [5.7; 11.7]	16 (5.2%) [3; 8.4]	.04*
Depressive disorder	24 (4.3%) [2.8; 6.4]	17 (4.7%) [2.8; 7.5]	36 (11.8%) [8.4; 16]	< .001*
Other	63 (11.4%) [8.9; 14.3]	76 (21.2%) [17.1; 25.8]	67 (22%) [17.4; 27]	< .001*

Data are shown as frequency (percentage) and [95% confidence interval], except for "new comorbidities per participant," which is mean (standard deviation) and [95% confidence interval]. **P* value is statistically significant after Benjamini-Hochberg correction.

(15.9% vs 9.5%), ischemic heart disease (14.5% vs 4.9%), and chronic kidney disease (21.7% vs 10.5%). It also showed a higher incidence of chronic obstructive pulmonary disease (9.7% vs 4.9%) and solid neoplasms (8.4% vs 5.2%). Compared with cluster 2, cluster 3 presented a significantly higher incidence of depressive disorder (11.8% vs 4.7%) (**Table 3**).

At the end of follow-up, the baseline differences in chronic medicine prescription between the clusters persisted (**Table 4**). Cluster 1 showed the lowest frequency of all medications. Cluster 2 had a significantly higher intake of medication related to cardiovascular risk factors and disease with respect to the other clusters, while cluster 3 had a significantly higher intake of nonsteroidal anti-inflammatory drugs, weak opioids, antidepressants, anxiolytics, hypnotics, and sedatives than the other clusters. The use of bronchodilators was similar in these two clusters. Strong opioids and corticosteroids were the only medications that did not show a significant difference between groups at baseline, but at the end of follow-up their use was significantly higher in clusters 2 and 3 compared to cluster 1.

Mortality, hospitalizations, and causes of hospital admission are depicted in **Table 5**. The percentage of participants who required any hospital admission and the number of hospitalizations per person were similar in clusters 2 and 3 [60.2% and 1.9 (2.7) vs 60.7% and 1.5 (2.3), respectively] but were significantly higher than in cluster 1 [38.7% and 0.7 (1.3), $P < .001$]. There were significant differences in some of the causes of hospitalization: Cluster 2 showed the highest rates of hospitalizations caused by heart failure (15%), ischemic heart disease (5.3%), and digestive (8.6%) and kidney disease (6.1%), whereas cluster 3 presented a significantly higher rate of admissions caused by traumatological problems (18%). Hospitalization because of respiratory, vascular, neoplastic, infectious, and ophthalmological reasons were significantly lower in cluster 1 than in the other clusters. Mortality at 5 years was significantly higher in cluster 2 compared to both cluster 3 and cluster 1 (12.3%, 5.9%, and 2.2%, respectively; $P < .001$). There were no statistically significant differences in the cause of death between the three groups (**Table S2**).

Effect of CPAP treatment in the different clusters

CPAP treatment was prescribed to 237 participants in group 1 (42.8%), 246 in group 2 (68.5%), and 139 (45.5%) in group 3. At the end of follow-up, 443 participants (36.4%) were receiving active CPAP treatment (31.3% of cluster 1, 48.5% of cluster 2, and 31.5% of cluster 3) and the actual compliance with CPAP in each group was 72.9% (n = 173/237), 70.7% (n = 174/246), and 69% (n = 96/139), respectively.

In clusters 1 and 3 there were no significant differences between CPAP and No CPAP users in the incidence of comorbidities, prescription of chronic medication, hospital admissions,

Table 4—Medicine prescription at the end of follow-up in each cluster.

Medication	Cluster 1	Cluster 2	Cluster 3	*P**
Beta blockers	38 (6.9%) [4.9; 9.3]	168 (46.8%) [41.5; 52.1]	44 (14.4%) [10.7; 18.9]	< .001
Calcium blockers	36 (6.5%) [4.6; 8.9]	132 (36.8%) [31.8; 42]	68 (22.3%) [17.7; 27.4]	< .001
Angiotensin-converting enzyme inhibitors	151 (27.3%) [23.6; 31.2]	279 (77.7%) [73.1; 81.9]	186 (61%) [55.3; 66.5]	< .001
Diuretics	62 (11.2%) [8.7; 14.1]	164 (45.7%) [40.4; 51]	108 (35.4%) [30; 41.1]	< .001
Antihypertensives	9 (1.6%) [0.7; 3.1]	42 (11.7%) [8.6; 15.5]	19 (6.2%) [3.8; 9.6]	< .001
Lipid-lowering agents	122 (22.1%) [18.7; 25.8]	248 (69.1%) [64; 73.8]	187 (61.3%) [55.6; 66.8]	< 0.001
Oral hypoglycemic agents	42 (7.6%) [5.5; 10.1]	165 (46%) [40.7; 51.3]	59 (19.3%) [15.1; 24.2]	< .001
Insulins	10 (1.8%) [0.9; 3.3]	73 (20.3%) [16.3; 24.9]	14 (4.6%) [2.5; 7.6]	< .001
Antiarrhythmics	8 (1.4%) [0.6; 2.8]	28 (7.8%) [5.2; 11.1]	19 (6.2%) [3.8; 9.6]	< .001
Antiplatelets	52 (9.4%) [7.1; 12.1]	172 (47.9%) [42.6; 53.2]	84 (27.5%) [22.6; 32.9]	< .001
Anticoagulants	19 (3.4%) [2.1; 5.3]	69 (19.2%) [15.3; 23.7]	37 (12.1%) [8.7; 16.3]	< .001
Vasodilators for cardiac diseases	5 (0.9%) [0.3; 2.1]	55 (15.3%) [11.8; 19.5]	21 (6.9%) [4.3; 10.3]	< .001
Bronchodilators	81 (14.6%) [11.8; 17.9]	119 (33.1%) [28.3; 38.3]	87 (28.5%) [23.5; 33.9]	< .001
Anxiolytics	79 (14.3%) [11.5; 17.5]	69 (19.2%) [15.3; 23.7]	124 (40.7%) [35.1; 46.4]	< .001
Antidepressants	114 (20.6%) [17.3; 24.2]	89 (24.8%) [20.4; 29.6]	182 (59.7%) [53.9; 65.2]	< .001
Hypnotics and sedatives	22 (4%) [2.5; 6]	19 (5.3%) [3.2; 8.1]	38 (12.5%) [9; 16.7]	< .001
Nonsteroidal anti-inflammatory drugs	173 (31.3%) [27.4; 35.3]	113 (31.5%) [26.7; 36.6]	174 (57%) [51.3; 62.7]	< .001
Corticosteroids	26 (4.7%) [3.1; 6.8]	32 (8.9%) [6.2; 12.4]	20 (6.6%) [4.1; 9.9]	.04
Weak opioids	32 (5.8%) [4; 8.1]	59 (16.4%) [12.8; 20.7]	82 (26.9%) [22; 32.2]	< .001
Strong opioids	10 (1.8%) [0.9; 3.3]	19 (5.3%) [3.2; 8.1]	22 (7.2%) [4.6; 10.7]	< .001

Data are shown as frequency (percentage) and [95% confidence interval]. **P* values shown are statistically significant after Benjamini-Hochberg correction.

Table 5—Mortality and hospital admissions in each cluster during follow-up.

	Cluster 1	Cluster 2	Cluster 3	*P*
Mortality	12 (2.2%) [1.1; 3.8]	44 (12.3%) [9; 16.1]	18 (5.9%) [3.5; 9.2]	< .001
Number of hospitalizations per participant	0.7 (1.3) [0.6; 0.8]	1.9 (2.7) [1.6; 2.2]	1.5 (2.3) [1.2; 1.8]	< .001
Number of participants that required hospitalization	214 (38.7%) [34.6; 42.9]	216 (60.2%) [54.9; 65.3]	185 (60.7%) [54.9; 66.2]	< .001
Causes of hospitalization				
Heart failure	6 (1.1%) [0.4; 2.3]	54 (15%) [11.5; 19.2]	18 (5.9%) [3.5; 9.2]	< .001
Ischemic heart disease	5 (0.9%) [0.3; 2.1]	19 (5.3%) [3.2; 8.1]	3 (1%) [0.2; 2.8]	< .001
Respiratory	21 (3.8%) [2.4; 5.7]	45 (12.5%) [9.3; 16.4]	24 (7.9%) [5.1; 11.5]	< .001
Vascular	3 (0.5%) [0.1; 1.6]	9 (2.5%) [1.2; 4.7]	7 (2.3%) [0.9; 4.7]	.04
Kidney disease	3 (0.5%) [0.1; 1.6]	22 (6.1%) [3.9; 9.1]	7 (2.3%) [0.9; 4.7]	< .001
Digestive	17 (3.1%) [1.8; 4.9]	31 (8.6%) [5.9; 12]	13 (4.3%) [2.3; 7.2]	< .001
Infectious	23 (4.2%) [2.7; 6.2]	44 (12.3%) [9; 16.1]	29 (9.5%) [6.5; 13.4]	< .001
Neoplastic	30 (5.4%) [3.7; 7.7]	37 (10.3%) [7.4; 13.9]	28 (9.2%) [6.2; 13]	.03
Ophthalmological	33 (6%) [4.1; 8.3]	42 (11.7%) [8.6; 15.5]	33 (10.8%) [7.6; 14.9]	.01
Traumatological	37 (6.7%) [4.8; 9.1]	38 (10.6%) [7.6; 14.2]	55 (18%) [13.9; 22.8]	< .001

Data are shown as frequency (percentage) and [95% confidence interval], except for "Number of hospitalizations per participant" which is mean (standard deviation) and [95% confidence interval]. There were no statistically significant differences in the cause of death between the three groups. Only causes of hospitalization that were significantly different between the clusters after Benjamini-Hochberg correction are shown. Other causes of hospitalization in which no significant differences were observed between the clusters were cerebrovascular disease, neurological, surgical, metabolic, toxic, hematological, urologic, psychiatric, pulmonary embolism, and autoimmune diseases.

or mortality (**Table S3**, **Table S4**, **Table S5**, and **Table S6**). In cluster 2, all-cause mortality was significantly higher in No CPAP users compared to CPAP users (20% vs 4%; $P < .001$, **Table 6**) but there were no differences in the cause of death (**Table S6**). Both groups showed a similar number of hospitalizations, but heart failure was a cause significantly higher in the No CPAP group (21.1% vs 8.6%, $P = .002$, **Table S5**). No significant differences were observed in the incidence of comorbidities or the prescription of chronic medication (**Table S3** and **Table S4**).

Results from Cox proportional hazards are summarized in **Table 7** and **Figure 1**.

Although comparison of mortality within clusters, using the Kruskall-Wallis test, showed a difference in mortality only in cluster 2, the Cox multivariate analysis was able to reveal that mortality among patients not treated with CPAP was significantly increased in all clusters.

Individuals who did not receive CPAP treatment were at increased risk of death when compared with those who were treated with CPAP (hazard ratio 5.84, confidence interval

Table 6—Effect of CPAP treatment in each cluster.

	Cluster 1			Cluster 2			Cluster 3		
	CPAP	No CPAP	*P*	CPAP	No CPAP	*P*	CPAP	No CPAP	*P*
Number of participants	173 (31.3%)	380 (68.7%)		174 (48.5%)	185 (51.5%)		96 (31.5%)	209 (68.5%)	
New comorbidities per participant	0.8 (1.1) [0.7; 1]	0.8 (1) [0.7; 0.9]	.544	1.2 (1.3) [1; 1.4]	1.1 (1.2) [1; 1.3]	.74	1.1 (1) [0.9; 1.4]	1.1 (1.1) [0.9; 1.2]	.362
Deaths	0 (0%) [0; 2.1]	12 (3.2%) [1.6; 5.5]	.022	7 (4%) [1.6; 8.1]	37 (20%) [14.5; 26.5]	< .001*	2 (2.1%) [0.3; 7.3]	16 (7.7%) [4.4; 12.1]	.098
Number of hospitalizations per participant	0.6 (1.1) [0.5; 0.8]	0.8 (1.4) [0.6; 0.9]	.402	1.4 (2.2) [1.1; 1.7]	2.3 (3.1) [1.8; 2.7]	.013	1 (1.2) [0.8; 1.2]	1.7 (2.6) [1.4; 2.1]	.038
Total number of participants that required hospitalization	63 (36.4%) [29.2; 44.1]	151 (39.7%) [34.8; 44.9]	.516	99 (56.9%) [49.2; 64.4]	117 (63.2%) [55.9; 70.2]	.263	52 (54.2%) [43.7; 64.4]	133 (63.6%) [56.7; 70.2]	.148

Data are shown as frequency (percentage) and [95% confidence interval] for categorical variables and as mean (standard deviation) and [95% confidence interval] for continuous variables. **P* value is statistically significant after Benjamini-Hochberg correction. CPAP = continuous positive airway pressure.

Table 7—Cox proportional hazards models assessing all-cause mortality.

	HR	95% CI	*P*
CPAP users vs No CPAP	5.84	2.9–11.8	< .001
Cluster 2	7.7	4.06–14.63	< .001
Cluster 3	2.79	1.34–5.79	.006

CI = confidence interval, CPAP = continuous positive airway pressure, HR = hazard ratio.

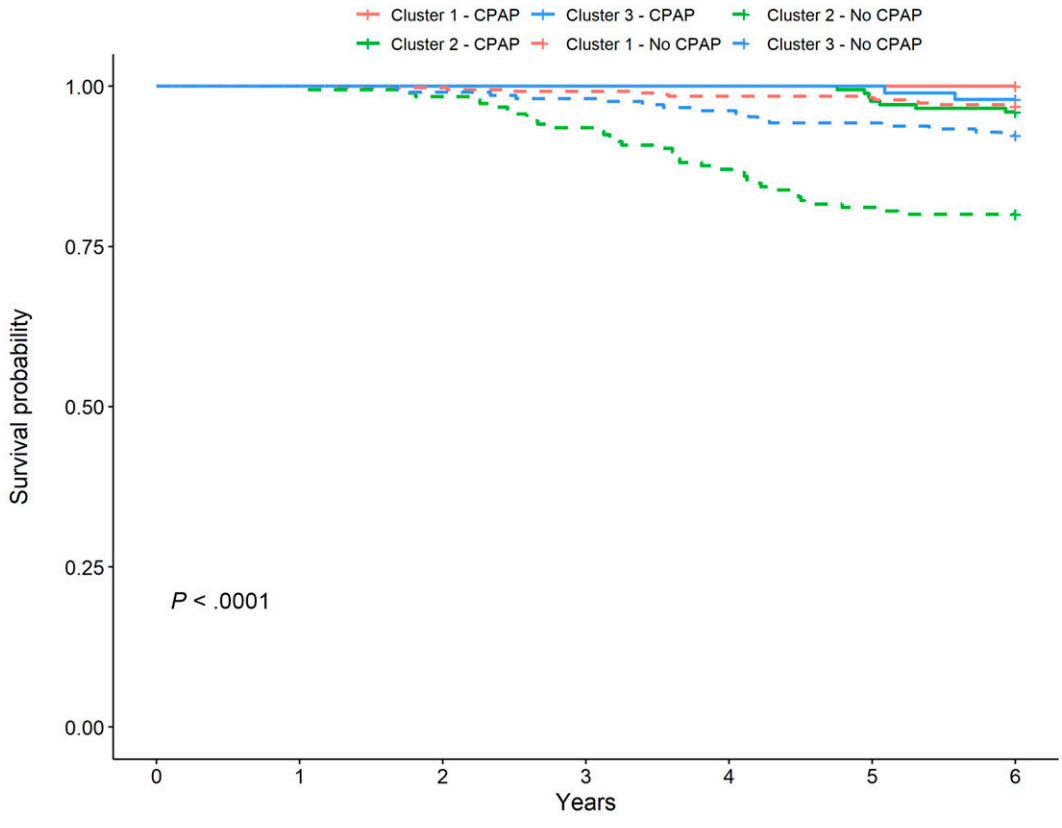
2.9–11.8, $P < .001$). The difference in mortality, according to CPAP treatment, was observed from the second year of follow-up. This risk was higher in clusters 2 and 3, compared with cluster 1 (hazard ratio 7.7, confidence interval 4.06–14.63, $P < .001$ and hazard ratio 2.79, confidence interval 1.34–5.79, $P = .006$, respectively).

DISCUSSION

We identified three distinctive OSA phenotypes with particular clinical implications: two predominantly male clusters, differentiated by age, BMI, OSA severity, cardiovascular risk factors and disease, and a third cluster constituted mainly by female participants with moderate OSA, cardiovascular risk factors, and a high prevalence of depression, anxiety, insomnia, and chronic pain. The baseline characteristics of each cluster maintained the same trend over time regarding the incidence of new comorbidities, medication intake, hospitalization rates, and reasons for admission. The absence of CPAP treatment and the cluster subtype were associated with a higher risk of mortality from all causes.

Our study is original for two main reasons. First, we included a broad spectrum of chronic medicine prescriptions for clustering. The inclusion of chronic medication was useful not only to define the different groups but also to strengthen the accuracy of the diagnoses, to uncover a higher prevalence of the diagnoses of depression and insomnia than those documented by the

Figure 1—Kaplan-Meier estimate.



Kaplan-Meier survival probability curves for all-cause mortality. Dotted lines represent the No CPAP groups. CPAP = continuous positive airway pressure.

physician, and to bring to light new information on a high prevalence of chronic pain in the female-predominant cluster. Although several OSA cluster analyses have identified phenotypes using information about comorbidities,[3,5,16,17] so far only Quan et al have used medications as part of the defining variables. However, these authors limited medications to those related to cardiovascular risk factors or disease.[9] Second, few studies have performed a longitudinal follow-up of phenotypes defined through cluster analysis. Most of them have focused on cardiovascular outcomes and mortality and the influence of CPAP treatment.[6,8,9,18] Their results are not comparable to ours since their clusters are defined very differently. Importantly, OSA's comorbidity burden is not just limited to cardiovascular disease but is also associated with diseases of a different nature like metabolic, respiratory, kidney, and liver diseases and psychological conditions.[19] Few studies have analyzed other aspects in the long term. Gagnadoux et al examined CPAP treatment success in the different clusters at 6 months, defined by a CPAP use ≥ 4 hours, a decrease in ESS, or an increase in the energy/vitality component score of the Short Form 36 questionnaire. They found a similar female cluster with high rates of depressive symptoms with a low likelihood of CPAP treatment success.[7] Pien et al studied treatment response patterns, BMI, quality of life, and comorbidities during 2 years, in clusters defined mainly by symptomatology.[10] Our study, analyzing for 5.8 years multiple comorbidities, chronic medication related to a variety of pathologies, hospital admissions, and mortality, plus the influence of CPAP, provides more comprehensive information, not restricted to the cardiovascular field. It also allows for the validation of the phenotypes: Their baseline features did not represent just a temporary finding and had different prognostic value. So far, no other cluster analysis has carried out such a complete descriptive study of OSA phenotypes in the long term.

Differences between clusters 1 and 2, the predominantly male clusters, could be explained by the age difference. Both groups likely represent the evolution of the classical OSA patient: men of middle age with overweight, some cardiovascular risk factors, and moderate OSA who, a decade later, have gained weight, are obese, have severe OSA, and start developing cardiovascular disease, with increased related medication intake. Cluster 2 also stood out for having the highest incidence of chronic kidney disease and the greatest number of hospital admissions for this reason. Assuming that cluster 2 represents the natural evolution of cluster 1, approximately 10–15 years later, this enhances the need for improving the management of younger and middle-aged patients with moderate OSA, regarding comprehensive lifestyle and weight-loss interventions, among others. At baseline, clusters 2 and 3 had a prevalence of solid neoplasms (6.4% and 5.9%, respectively) which were significantly higher than that observed in cluster 1 (3.1%), which could be explained by the older age of these clusters (63.4 in cluster 2, 64.5 in cluster 3 vs mean 51.1 years in cluster 1). However, at follow-up, cluster 2 showed a significantly higher incidence of solid neoplasms (8.4% vs 4.3% in cluster 1 and 5.2% in cluster 3, $P = .04$). As age was similar in clusters 2 and 3, other characteristics in patients of group 2 (eg, worse baseline BMI, comorbidities, OSA severity, etc) might explain the greater incidence of solid neoplasms observed in this group during the follow-up.

Cluster 3, the "female" cluster, showed the highest prevalence and incidence, during follow-up, of depressive disorder (15.7% and 11.8%, respectively). However, the much higher consumption of antidepressants (55.1%) and anxiolytics (40%), which persists at the end of follow-up, suggests a higher real prevalence of depression and anxiety than that obtained by disease-coding and also than that described in the general Spanish population.[20] In addition, this cluster showed a significant intake of hypnotics and sedatives (11.1%), despite the fact that insomnia had a very low prevalence in our cohort (falling in the "Other" diagnostic category). Other cluster analyses have found similar predominantly female phenotypes with symptoms of insomnia or "disturbed sleep,"[4–6] depression, obesity, and associated comorbidities (hypertension and type 2 diabetes).[7] A new finding not previously reported was a high prescription of nonsteroidal anti-inflammatory drugs (67.9%) and weak opioids (15.1%) in cluster 3, suggesting that chronic pain could be related to poor sleep and alert about OSA suspicion. This phenotype also had the highest rate of hospitalizations for traumatological reasons. No differences were observed in the incidence of comorbidities or medication intake at the end of follow-up.

During the 5-year follow-up, the absence of CPAP treatment was associated with increased mortality risk. We also observed a reduction in heart failure hospital admissions in the CPAP users only in the older-men phenotype. The risk of mortality was significantly higher in patients not treated with CPAP (CPAP not prescribed or discontinued), compared to those who received this treatment, and this risk was stronger in clusters 2 and 3 compared to 1. This supports the importance of treating moderate-to-severe OSA with CPAP, but it also raises the need for early consideration of alternative options to CPAP in those younger with moderate OSA and without comorbidities or hypersomnolence, and in those not willing to use this treatment, as we are in an era where there are multiple reasonable treatment modalities for OSA.[21]

The older clusters with comorbidities showed a greater benefit from CPAP compared to the younger (and healthier) one. Jennum et al in a prospective cohort, described a more significant effect of CPAP treatment in mortality in patients aged ≥ 60 years than in those younger (40-59 years).[22] Nonetheless, recently published randomized controlled trials on the effect of CPAP on the secondary prevention of cardiovascular events and death in patients with OSA have led to negative results,[23–25] even though methodological biases have been suggested as likely explanations.[26] Clusters 1 and 3 had moderate OSA. Some studies have found only in severe OSA[27] a protective role of CPAP on cardiovascular events, but others have found it also in mild and moderate disease.[28,29] A meta-analysis of cohort studies that included participants within a wide age range (from 45 to 81 years old) found that severe, but not mild or moderate OSA, increased the risk for both all-cause mortality and cardiovascular mortality, and that CPAP treatment significantly reduced this risk.[30] Our study further suggests a significant effect of CPAP treatment on mortality, especially strong in the older male cluster with severe OSA and comorbidities.

The predominantly female cluster was benefited from CPAP treatment but to a lesser extent than the older-men cluster. Previous cohort studies have shown reduced mortality in OSA male patients treated with CPAP,[27] but mortality in female patients with OSA has been much less studied than in men, with different findings. In a prospective, observational cohort study on 1116 women, Campos-Rodriguez et al concluded that severe OSA was associated with cardiovascular death in women, and adequate CPAP treatment may reduce this risk.[31] Another recent long-term prospective clinical cohort study found that CPAP therapy was associated with reduced all-cause mortality in both men and women.[28] On the other side, Jennum et al, in a large study from the Danish National Patient Registry, described that female patients with OSA had lower mortality than males, irrespective of whether they received CPAP treatment.[22] Few studies focusing on women have analyzed other CPAP outcomes, like those related to the quality of life, with inconsistent results.[7,32] Our findings support the importance of addressing OSA in women with a different approach regarding clinical suspicion and treatment outcomes and the beneficial effect of CPAP therapy in older women with comorbidities.

Even though 72.4% of the participants had moderate to severe OSA, only 25% of our patients presented excessive daytime sleepiness, a result consistent with a reported prevalence of this symptom of 18.7%, in the European Sleep Apnea Cohort.[33]

CPAP was prescribed in a higher percentage of patients of group 2 due to worse OSA severity and because patients with moderate OSA without daytime sleepiness are considered less suitable for CPAP treatment in the Spanish guidelines.[14] CPAP compliance was similar in the 3 groups in those patients who continued treatment at follow-up.

Our study has strengths and limitations. Our cohort is composed of a large number of participants and covers a relatively wide age and OSA severity range. Unlike previous studies, the cohort had a significant female representation, which ensures its having considered sex-related issues. We also used a large number of variables and a robust statistical method for clustering. A detailed follow-up was performed for a valuable number of years. Although no study based on electronic medical records is exempt from coding errors or reporting biases, the information on comorbidities, medicine prescriptions, hospitalizations, and mortality rates, collected from primary care and hospital settings through an official entity such as Agency for Health Quality and Assessment of Catalonia, ensure that it is trustworthy. Although we do not have detailed information on symptoms, unlike previous cluster analyses[3,4,6] we have used the ESS, the most common tool in all studies and clinical practice to assess the degree of sleepiness, which together with the data on comorbidities and chronic medications provides objective data and real-life information that enhances the reliability of our results. One limitation of our study is the indistinctive use of respiratory polygraphy and full polysomnography for the diagnosis of OSA, which could have underestimated the severity of OSA in the patients diagnosed with the first method. However, our results reflect routine clinical practice in Europe.[34] If full polysomnography had been used in all patients, the severity of OSA would probably still be worse in cluster 2 with respect to clusters 1 and 3.

Another limitation is that we did not have information on the cause of death of participants dying outside the hospital setting, which might have underestimated the proportion of deaths of cardiovascular or cerebrovascular origin. Finally, cluster analyses are descriptive: They do not permit us to establish a cause–effect relationship, but they serve to identify homogeneous groups and unknown patterns of associations among a large number of variables.

In conclusion, we identified three different clusters with different outcomes in a 5-year follow-up. The two clusters of predominantly men could correspond to the same group evolving from middle-aged with moderate OSA to older men with severe OSA and comorbidities. A female-predominant cluster with moderate OSA, depression, anxiety, insomnia, and chronic pain generates a need for future research, improving clinical recognition and management of this phenotype. In older clusters with comorbidities, the risk of mortality is increased among those patients not treated with CPAP. Early intervention to promote and ensure management of OSA in middle-aged men with mild-to-moderate OSA, without sleepiness, and a low comorbidity burden is needed.

Further studies are needed to reproduce our findings and to confirm the clinical relevance, prognostic value, and treatment response of these phenotypes.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
CPAP, continuous positive airway pressure
CT90%, percentage of time with SaO2 below 90%
ESS, Epworth Sleepiness Scale
OSA, obstructive sleep apnea

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Address correspondence to: Patricia Lloberes, MD, PhD, Servicio de Neumología, Hospital Universitario Vall d'Hebron, Passeig de la Vall d'Hebron 119, 08035, Barcelona, Spain; Email: patricialloberes@yahoo.es

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