Universitat Autònoma de Barcelona

IDENTIFICATION AND VALIDATION OF PHENOTYPES IN A COHORT OF PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

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Doctoral Thesis

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LIST OF ABBREVIATIONS

AHI	apnea-hypopnea index
BMI	body mass index
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CT90%	percentage of time with oxygen saturation below 90%
EDS	excessive daytime sleepiness
ESS	Epworth sleepiness scale
ODI	oxygen desaturation index
OHS	obesity hypoventilation syndrome
OSA	obstructive sleep apnea
$PaCO_2$	partial carbon dioxide arterial pressure
PAM	partition around medoids
PAP	positive airway pressure
RCT	randomized controlled trial
REM	rapid eye movement
SaO_2	oxygen saturation
SDB	Sleep-disordered breathing

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ABSTRACT

Introduction

Obstructive sleep apnea (OSA) is a heterogeneous, complex disease, associated with multiple comorbidities. This study aims to identify OSA phenotypes through cluster analysis, perform a long-term follow-up to validate the phenotypes, and assess the influence of continuous positive airway pressure (CPAP) treatment in the different groups.

Methods

We applied a partitioning around Medoids technique in a cohort of 1,217 patients 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 CPAP treatment in these regards.

Results

We identified three phenotypes: two predominantly male clusters, one composed of middle-aged patients with overweight, moderate OSA, and cardiovascular risk factors and the other consisting of older, obese patients 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 and 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 CPAP 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 particular clinical features that maintained differentiated characteristics during follow-up. The absence of CPAP treatment and the cluster subtype were associated with higher mortality risk from all causes.

RESUMEN

Introducción

La apnea obstructiva del sueño (AOS) es una enfermedad heterogénea, compleja, que se asocia a múltiples comorbilidades. El objetivo de este estudio es identificar fenotipos de AOS a través de un análisis de clúster, realizar un seguimiento a largo plazo para validar dichos fenotipos y evaluar la influencia del tratamiento con presión positiva continua en las vías aéreas (CPAP) en los distintos grupos.

Métodos

Aplicamos una técnica de Partición Alrededor de Medoids en una cohorte de 1.217 pacientes recientemente diagnosticados con AOS. Realizamos un seguimiento a 5 años, analizando la incidencia de comorbilidades, la medicación crónica, las hospitalizaciones, la mortalidad y la influencia del tratamiento con CPAP en estos aspectos.

Resultados

Identificamos tres clústeres. Dos compuestos predominantemente por hombres: uno formado por pacientes de mediana edad, con sobrepeso, AOS moderado y factores de riesgo cardiovascular; otro compuesto por pacientes de mayor edad, con obesidad, AOS severo, factores de riesgo cardiovascular y una alta prevalencia de cardiopatía isquémica (18.4%) y fibrilación auricular (9.7%). El tercer clúster está compuesto en un 77% por mujeres, con AOS moderado, factores de riesgo cardiovascular, una alta prevalencia de depresión (15.7%), así como una alta prescripción de medicamentos antidepresivos (55.1%), ansiolíticos (40.0%), hipnóticos y sedantes (11.1%), antiinflamatorios no esteroideos (67.9%) y opioides débiles (15.1%). Cada clúster mantuvo sus características basales durante el seguimiento, en relación a la incidencia de comorbilidades, consumo de medicamentos, hospitalizaciones y motivos de ingreso. La ausencia de tratamiento con CPAP se asoció a un mayor riesgo significativo de mortalidad por cualquier causa (hazard ratio 5.84, intervalo de confianza 2.9–11.8), especialmente en el clúster compuesto por hombres de mayor edad (hazard ratio 7.7, intervalo de confianza 4.06–14.63) y en el de mujeres (hazard ratio 2.79, intervalo de confianza 1.34–5.79).

Conclusiones

Identificamos tres fenotipos con características clínicas particulares que se han mantenido durante el seguimiento. La ausencia de tratamiento con CPAP y el tipo de clúster se han asociado a mayor mortalidad por cualquier causa.

1. INTRODUCTION

INTRODUCTION

Obstructive sleep apnea (OSA) is a pathology characterized by repetitive episodes of partial or complete obstruction of the upper airway during sleep that lead to intermittent hypoxemia, changes in intrathoracic pressure, and arousals from sleep. It is highly prevalent in the adult population worldwide[1], especially in subjects with overweight or obesity[2].

OSA is a significant cause of excessive daytime sleepiness, cognitive dysfunction, impaired work performance, and impaired quality of life[3]. It is associated with higher mortality and multiple comorbidities such as hypertension, type 2 diabetes, atrial fibrillation, heart failure, coronary heart disease, stroke, and cancer[4].

Positive airway pressure (PAP) is the primary treatment for OSA: it reduces disease severity, sleepiness, blood pressure, motor vehicle accidents and improves the sleep-related quality of life[5]. However, there is insufficient evidence to prove that PAP reduces cardiovascular events or mortality.[5]

Understanding OSA's pathophysiology, its link to the multiple associated comorbidities, as well as finding effective treatments to reduce the risk of morbidity and mortality, are still a challenge that requires further research. Personalized medicine strategies, like phenotyping, could help define diagnosis and treatment strategies, optimize resources, and improve the management of the disease.

This study aims to identify OSA phenotypes performing a cluster analysis on multiple clinical variables and OSA severity measures, to validate them performing a long-term follow-up, and to assess the impact of treatment in each group.

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The results have been presented in the 25th Congress of the European Sleep Research Society.

It has led to two publications: an editorial published in Archivos de Bronconeumología (the official journal of the Spanish Respiratory Society of Pulmonology and Thoracic Surgery: IF 4.872, Q2) and an original article published in the Journal of Clinical Sleep Medicine (the official journal of the American Academy of Sleep Medicine (AASM): IF 4.062, Q2).

1.1 EPIDEMIOLOGY

The prevalence of OSA varies in the general population according to age, sex, and diagnosis criteria. The apnea-hypopnea index (AHI) is defined as the number of apneas and hypopneas present per hour of sleep and defines the presence and severity of OSA. Over the years, the use of nasal pressure sensors rather than only thermistors, the improvement of pulse oximeters and the changes in the coding criteria, especially of hypopneas, partially explain the different prevalences registered in epidemiological studies.

One of the first OSA population studies was the Wisconsin Cohort, published in 1993. Diagnostic of OSA was made by polysomnography, defining hypopneas as any reduction in airflow and a 4% decline in blood oxygen saturation. Performed on a random sample of 602 employed men and women, 30 to 60 years old, it showed a prevalence of OSA (AHI≥5) of 24% in men and 9% in women, and symptomatic OSA (i.e., associated with daytime hypersomnolence) of 4% in men and 2% in women[6]. Years later, between 2007 and 2010, using data from the same cohort, the estimated prevalence of OSA among participants 30 to 70 years old was 33.9% in men and 17.4% in women, and of symptomatic OSA 14.3% in men and 5% in women. The increased prevalence over the last two decades (relative increases of between 14% and 55% depending on the subgroup) was attributed to the obesity epidemic in the United States[7].

In Spain, a study performed between 1993 and 1997, among a population 30 to 70 years old, found an AHI≥5 in 26.2% of men and 28% of women, and an AHI≥15 (moderate to severe OSA) in 14.2% of men and 7% of women. Subjects were diagnosed by polysomnography using the 4% drop of blood oxygen saturation hypopnea's definition[8].

A more recent study (2015), in a population-based sample in Switzerland, of individuals 40 to 85 years old, used the latest scoring criteria from the AASM, where hypopnea was defined by a 3% drop in blood oxygen saturation and a 30% drop in airflow[9]. Their results showed an even higher prevalence: OSA (AHI≥5) was found in 83.3% of men and 60.8% of women, while moderate to severe OSA (AHI≥15) reached 49.7% and 23.4%, respectively. It was suggested that these high prevalences might be attributable to the increased sensitivity of current recording techniques and scoring criteria[10].

Globally, using the latest AASM scoring criteria[9], it was estimated that mild to severe OSA affects 936 million adults, 30 to 69 years old, and moderate to severe OSA affects 425 million[1].

OSA can be present in all age ranges, from newborns to the elderly, but its prevalence and severity increase with age, reaching a peak between the sixth and seventh decades of life[8,10–12].

It is between 2 and 3 folds more frequent in men than in women, although the prevalence increases from menopause in the latter, tending to equal that of men[10,13,14].

Overweight and obesity are important risk factors for OSA. Most epidemiological studies find an association between increasing body mass index (BMI) and a higher prevalence of OSA[7,10]. A population-based cohort, in subjects 20 to 80 years old, found that the prevalence of moderate-severe OSA was 10.7% in men and 2.6% in women who were normal weight (BMI <25Kg/m^2), 21.2% and 9.1% in subjects with overweight (BMI 25-30Kg/m^2), and 62.6% and 21.8% in subjects with obesity (BMI ≥ 30Kg/m^2)[2]. In the Wisconsin Sleep Cohort, the prevalence of OSA among individuals 50 to 70 years old with a BMI ≥25Kg/m^2 was 18.9% in men and 9.3% in women, increasing to 61.4% and 41.1% in men and women with a BMI between 30 and 39.9 Kg/m^2 [7].

Upper airway structure and craniofacial abnormalities are also risk factors for OSA[15,16]. Some examples include dysmorphisms related to mandibular or maxillary size and position, narrowed nasal cavities, and tonsillar or adenoid enlargement, the latter especially in children[17].

Chronic nasal congestion at night, regardless of the cause, is associated with a higher risk of OSA both in experimental and epidemiological studies[18]. Subjects with chronic nasal congestion are 1.8 times more likely to have moderate to severe OSA than those without nasal congestion[19].

Smoking also favors the development of OSA. It has been observed that current cigarette smokers were three times more likely to develop OSA than former or never smokers, heavy smokers had the greatest risk, and former smoking was not related to OSA[20].

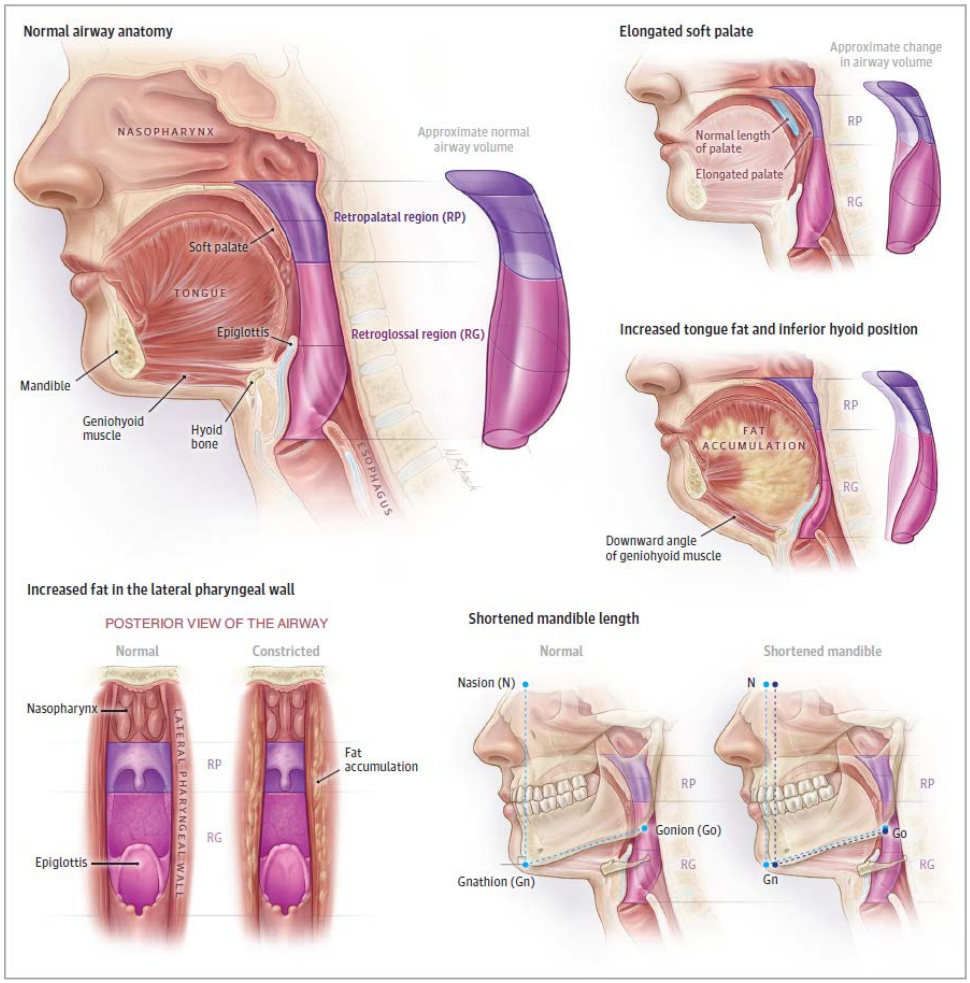
There is a higher risk of OSA in relatives of subjects with OSA. This association could be explained by similar lifestyles or environmental factors and genetic predisposition. Genetic factors could determine craniofacial structures[21], body fat distribution, and neural control of the upper airway muscles. It has been estimated that familial factors may explain 40% of the variance of the AHI[22].

1.2 PATHOPHYSIOLOGY

OSA is a disorder characterized by repetitive episodes of upper airway collapse during sleep that interrupt the airflow partially (hypopneas) or completely (apneas), despite respiratory effort. The ability of the upper airway to remain open or to obstruct during sleep is determined by the balance between the anatomy of the upper airway, the muscle function and the degree of response to breathing changes during sleep.

The craniofacial structure is one of the most important determinants of upper airway patency during sleep. Obstruction of the upper airway due to narrowing can be found in the presence of retrognathia, tonsillar hypertrophy, inferiorly positioned hyoid bone, maxillary and mandibular retroposition, and decreased posterior airway space[23]. Some studies have found that OSA subjects have an enlarged volume of the soft tissue structures surrounding the upper airway because of fat deposition, including a larger volume of the tongue and lateral pharyngeal walls[24,25].

Figure 1. Anatomic Features Contributing to Obstructive Sleep Apnea. Adapted from Gottlieb et al[26].



To keep the patency of the upper airway during inspiration, several interrelated muscular mechanisms are involved: contraction of the genioglossus (that contracts with each inspiration to prevent the posterior collapse of the tongue), the levator and tensor palatini muscles (that advance and elevate the soft palate) and the geniohyoid and stylopharyngeus muscles (which oppose medial collapse of the lateral pharyngeal walls)[27]. During sleep, there is a physiological loss in the ventilatory drive that causes a fall in the activities of the upper airway dilator muscles and the respiratory pump muscles[28]. This generates a decrease in ventilation and increased partial carbon dioxide arterial pressure ($PaCO_2$) that do not affect breathing in healthy subjects. In individuals with OSA, the anatomical deficits in the upper airway added to the reduction in the upper airway dilator muscle activity at sleep onset lead to an increase in airway resistance. The increased airway resistance leads to increased flow turbulence that causes fluttering of the soft palate and upper airway's soft tissue resulting in snoring and in partial or complete obstruction of the airway[29].

Another fact that influences the upper airway's patency and resistanceis rostral fluid shift in recumbency. An increased vascular volume in the neck can favor upper airway obstruction by increasing its soft tissue volume and decreasing its caliber. Some studies show that displacement of fluid from legs to the neck increases neck circumference, decreases upper airway caliber[30], and increases upper airway collapsibility[31]. A study performed in nonobese healthy men suspected of OSA showed that overnight rostral fluid displacement from the legs was associated with an increase in neck circumference and the AHI[32]. This might be particularly relevant in OSA patients with high volume states like congestive heart failure, refractory hypertension, or kidney disease. A study in patients with uncontrolled hypertension and OSA found that intensified diuretic therapy reduced neck circumference and the mean AHI from 57.7 to 48.5[33].

Other non-anatomic factors can be involved in OSA development, like upper airway dilator muscle dysfunction, heightened chemosensitivity, and low arousal threshold (i.e., waking up from sleep prematurely, which could cause instability in ventilatory control)[34].

The systemic effects of OSA are a consequence of repetitive apneas and hypopneas.
Upper airway collapse leads to intermittent hypoxemia, changes in intrathoracic pressure, and arousals from sleep. Intermittent hypoxemia and carbon-dioxide retention increase sympathetic activity and release reactive oxygen species contributing to vascular disease, metabolic abnormalities, and inflammation[27]. Large intrathoracic pressure swings increase transmural pressure of all intrathoracic structures (atria, ventricles, intrathoracic aorta, and pulmonary vascular beds), produce changes in right ventricular preload, left ventricular overload,

myocardial oxygen consumption, and stroke volume[34]. Arousals from sleep generate sleep fragmentation, which is involved in the characteristic OSA's excessive daytime sleepiness and can also increase sympathetic activity, contributing to changes in blood pressure and heart rate. In this way, OSA triggers a cascade of hemodynamic, autonomic, chemical, inflammatory, and metabolic effects that promotes cardiovascular disease[35] and is involved in the development or exacerbation of multiple OSA-associated comorbidities.

1.3 CLINICAL PRESENTATION

One of the major and most frequent symptoms of OSA is daytime sleepiness. The AASM defines daytime sleepiness as the inability to stay awake and alert during the major waking episodes of the day, resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep[36]. Its prevalence varies among OSA populations, in part due to the different ways of evaluating it (e.g., questionnaires, Epworth Sleepiness Score (ESS), multiple sleep latency tests). While in some population studies, daytime sleepiness shows a prevalence of 14%[7], it might reach as high as 90% in clinical cohorts[37,38]. Frequently, OSA subjects report more problems with fatigue, tiredness, and lack of energy rather than sleepiness. In one study, when required to select the one most significant symptom, more patients chose lack of energy (about 40%) than any other problem, including sleepiness (about 22%)[39]. Daytime sleepiness is associated with poor work performance, traffic accidents, and reduced quality of life[40].

Snoring and associated symptoms like gasping or witnessed apneas are also frequent. A clinical OSA cohort found that the most prevalent symptom was snoring (100%)[38]. However, a systematic review that examined the accuracy of clinical examination found that while snoring had an 80-100% sensitivity for OSA diagnosis, specificity was below 46%. In this study, nocturnal choking or gasping was the most useful observation for identifying patients with OSA[41].

Other OSA symptoms include awakenings, associated or not to choking, as well as insomnia complaints. Some studies found a 30% prevalence of insomnia in OSA patients[42], being more frequent in women than in men[43]. A large European cohort of adult OSA patients showed that while daytime sleepiness (measured by an Epworth Sleepiness Score >10) was present in 44.4% of the subjects, sleep complaints suggestive of insomnia reached 53.5%[44].

Morning headaches have a variable prevalence in different reports, between 12% and 50% in OSA patients, doubling that of the general population[38,45]. They are a tension-type headache that occurs at least 15 days a month[45], and last several hours after awakening in the morning. Its etiology remains uncertain.

Another feature is the presence of nocturia (the need to void at least twice during nighttime sleep). Nocturia is more frequent in men with OSA than in the general population[46]. Patients with nocturia tend to be older and have more severe OSA[47].

Nocturnal gastroesophageal reflux is another common symptom in OSA patients. Some studies suggest that it is at least twice as common in OSA than in the general population, although there is controversy on whether OSA and nocturnal reflux are causally linked or merely associated

because of shared risk factors like obesity[48]. Additional symptoms that could be present in OSA are those related to associated comorbidities like resistant hypertension, type 2 diabetes mellitus, heart failure, atrial fibrillation, or neuropsychiatric symptoms.

1.4 DIAGNOSIS

OSA could be suspected by clinical presentation and physical examination, but it requires a sleep test for diagnostic confirmation.

Patient interrogation should include daytime sleepiness or fatigue, snoring, gasping or choking during sleep, witnessed apneas, nocturia, and morning headaches. Specific questionnaires have been developed to estimate the OSA risk:

- The Berlin questionnaire: designed for the primary care setting, it establishes the high or low risk of OSA according to questions on snoring behavior, sleepiness or fatigue, and obesity or hypertension history[49].
- The STOP-Bang questionnaire: the snoring, tiredness, observed apnea, high blood pressure - BMI, age, neck circumference, and gender questionnaire, developed as a screening tool in preoperative clinics. A score ≥3 has a 93% sensitivity in detecting moderate-severe OSA and 100% in severe OSA[50].
- The Epworth sleepiness scale: designed to measure daytime sleepiness through a self-reported questionnaire of 8 questions[51], is frequently used in clinical practice and research but has a low sensitivity for OSA diagnosis[52]. A value equal to or higher than ten is considered indicative of significant daytime sleepiness.

On physical examination, overweight and obesity are frequently found, but ~~a~~ normal weight does not rule out OSA[2,7]. Examination of the upper airway can help detect craniofacial abnormalities like retrognathia, tonsilar hypertrophy, macroglossia, elongated or enlarged uvula, high arched or narrow hard palate, or nasal abnormalities[53].

There are different classifications to quantify airway narrowing. The modified Mallampti classification was designed to assess difficult intubation. It scores the airway in 4 classes according to the relationship between the amount of mouth opening and the size of the tongue, providing an estimate of the space available for oral intubation[54]. The Friedman tongue position classifies the airway according to the visualization of the uvula, tonsils, soft and hard palate[55]. Both assessment techniques correlate with sleep apnea severity[56].

The diagnostic confirmation sleep test can be a laboratory-based polysomnography (PSG), the gold standard, or a home sleep apnea test.

PSG usually includes measures of airflow (by a nasal cannula and/or oral thermistor), snoring (through a microphone fixed over the trachea or nasal cannula), respiratory effort (by inductive thoracic and abdominal bands), oxygen hemoglobin saturation (by finger pulse oximetry),

registration of sleep stages and arousals (using electroencephalography, electrooculography, and electromyography), electrocardiography, body position, and leg movements. Home sleep apnea tests are simpler than PSG; most times sensors are self-applied by the patient at home and do not register sleep stages or leg movements. They typically record airflow, snoring, respiratory effort, arterial oxygen saturation, heart rate, and body position. Even though home sleep tests might underestimate the AHI because of its inability to register sleep stages and arousals (not registering respiratory effort related arousals, hypopneas defined by arousals, and estimating the AHI according to the recording time, rather than the total sleep time), they have a high sensitivity and specificity[57].

Based on the evidence of multiple studies that compared the accuracy of home sleep tests against PSG, the AASM recommends using PSG or home sleep test to diagnose OSA in uncomplicated adult patients presenting with signs and symptoms that indicate an increased risk of moderate to severe OSA[58]. An increased risk of moderate to severe OSA is defined by the presence of excessive daytime sleepiness and at least two of the following three criteria: regular loud snoring, witnessed apnea or gasping or choking, or diagnosed hypertension. If a single home sleep apnea test is negative, inconclusive, or technically inadequate, polysomnography should be performed for the diagnosis of OSA. A PSG is recommended in patients with significant cardiorespiratory disease, potential respiratory muscle weakness due to neuromuscular condition, awake hypoventilation or suspicion of sleep-related hypoventilation, chronic opioid medication use, history of stroke, or severe insomnia[58].

Diagnosis of OSA is made when any of the two following criteria are met[36]:

- There are 5 or more predominantly obstructive respiratory events (obstructive and mixed apneas, hypopneas, or respiratory effort-related arousals) per hour of sleep during a PSG or per hour of monitoring if using a home sleep test, and the presence of one or more of the following:
    - Sleepiness, nonrestorative sleep, fatigue, or insomnia symptoms.
    - Awakenings with breath holding, gasping, or choking.
    - The bed partner or other observer reports habitual snoring, breathing interruptions, or both during the patient's sleep.
    - The patient has been diagnosed with hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus.

- There are 15 or more predominantly obstructive respiratory events (apneas, hypopneas, or respiratory effort-related arousals) per hour of sleep (or monitoring) regardless of the presence of associated symptoms or comorbidities.

It should be noted that the concept of “respiratory effort-related arousal” is questioned since these types of events could be considered hypopneas. Currently, the Spanish Respiratory Society of Pulmonology and Thoracic Surgery’s international consensus recommends coding these types of events as hypopneas[59].

The severity of OSA has been established by expert consensus: an AHI less than 5 events per hour is considered normal, 5 to14.9 is mild, 15 to29.9 is moderate, and equal or higher than 30 is considered severe OSA[60]. Depending on the definition criteria of “hypopnea” there can be a great variance in the AHI[61], highlighting the importance of considering symptoms and comorbidities when making treatment decisions.

1.5 CONSEQUENCES OF OSA

OSA is associated with a higher risk of all-cause mortality, a high comorbidity burden, and impaired quality of life. Since OSA is a multifactorial disease and OSA patients are often affected by overweight/obesity, hypertension, type 2 diabetes, and dyslipidemia, it is unclear whether there is a direct cause-effect relationship between OSA and associated comorbidities or OSA acts as a mediator for the development or worsening of the different diseases[4,62]. OSA is also a well-recognized risk factor for motor vehicle and work-related accidents[63].

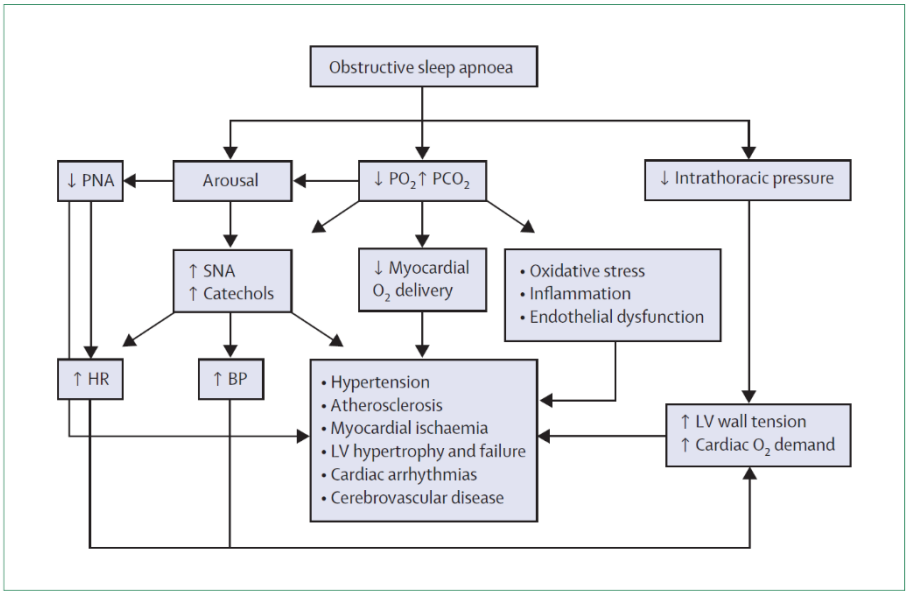
Following is a summary of the most studied conditions associated with OSA.

1.5.1 Cardiovascular comorbidities

Cardiovascular disease is one of the most common comorbidities associated with OSA. Several studies have found an association between OSA and a higher risk of all-cause mortality, cardiovascular morbidity, and mortality[64–67].

Multiple mechanisms have been proposed to explain the relationship between OSA and this comorbidity: intermittent hypoxia, high sympathetic nervous activity, endothelial cell dysfunction, oxidative stress, inflammation, accelerated atherosclerosis, swings in intrathoracic pressures[34,68]. However, OSA patients frequently are obese and have cardiovascular risk factors like hypertension or type 2 diabetes. So, despite the large number of studies that support a direct relationship between OSA and cardiovascular disease, there is still controversy about whether OSA directly impacts the development of cardiovascular disease or its association to it is just linked through common risk factors, like obesity.

Figure 2. Pathophysiological effects of obstructive sleep apnea on the cardiovascular system. Adapted from Bradley et al[35].



PNA: parasympathetic nervous system activity; PO_2: partial pressure of oxygen; PCO_2: partial pressure of carbon dioxide; SNA: sympathetic nervous system activity; HR: heart rate; BP:blood pressure; LV: left ventricular.

1.5.1.1 Hypertension

OSA is a recognized risk factor for arterial hypertension. The prevalence of hypertension in OSA patients varies from 35 to 80%[69]. Multiple clinical and community-based studies have found a higher risk of hypertension in OSA subjects than in the general population, which shows a dose-response relationship according to OSA's severity, independently of confounding factors like age and obesity[70–73]. A stronger association has been observed between OSA and resistant hypertension (blood pressure > 140/90 mm Hg using at least three blood pressure-lowering drugs, including a diuretic): a study found that the prevalence of OSA in patients with resistant hypertension was 71%, compared to 38% in patients with controlled hypertension[74].

Hypertension can occur during the 24 hours of the day, but OSA is especially associated with an absence in the normal reduction of blood pressure during night sleep (showing a non-dipper pattern)[75] which is associated with an increased cardiovascular risk. Some studies have found that OSA is more related to isolated diastolic or combined systolic/diastolic hypertension than isolated systolic hypertension[76].

CPAP (continuous positive airway pressure) treatment improves hypertension in OSA: several studies have found a reduction of systemic blood pressure, although the magnitude is usually small. A meta-analysis showed a reduction of 2.6 mmHg in systolic and 2.0 mmHg in diastolic

blood pressure, observing a greater reduction of systolic blood pressure, the higher the baseline AHI[77]. Even though the reduction is lower than the one obtained with antihypertensive drugs[78], it is clinically relevant since a reduction of 1-2mmmHg has been shown to reduce major cardiovascular events, like stroke and heart failure[79]. Patients with resistant hypertension have shown a greater reduction of blood pressure with CPAP treatment[80]. The beneficial effect of CPAP in OSA patients with hypertension has not been universal; for example, some studies have concluded that the reduction in blood pressure by CPAP treatment does not benefit nonsleepy OSA subjects[81–83].

1.5.1.2 Heart failure

The estimated prevalence of sleep-disordered breathing in patients with heart failure is 50%, although it can reach 78% in acutely decompensated heart failure[84–86]. Two types of sleep-disordered breathing might be found in heart failure patients: obstructive sleep apneas and central sleep apneas (frequently with Cheyne-Stokes breathing). The predominance of one or the other varies in the different studies and can be associated with either reduced or preserved left ventricular ejection fraction[34].

Several studies have shown that sleep-disordered breathing is a risk factor for heart failure and that the risk increases with greater severity of sleep-disordered breathing[65,87]. This association is not entirely clear in women[65]. In patients with heart failure, untreated OSA is associated with an increased risk of death independently of confounding factors[88].

1.5.1.3 Coronary heart disease

Marin et al., in a prospective cohort study of more than 1600 men with a 10-year follow-up, found that subjects with untreated severe OSA had a higher incidence of fatal and non-fatal cardiovascular events (including non-fatal myocardial infarction, non-fatal stroke, coronary artery bypass surgery, and percutaneous transluminal coronary angiography) compared to healthy participants, simple snorers, untreated patients with mild-moderate disease, and patients treated with CPAP, even after adjustment for confounding variables[89]. Numerous studies have supported these findings, showing an association between severe OSA and an increased risk of cardiovascular events, including coronary heart disease and mortality, independently of obesity and other shared risk factors[64,65,87,90]. The incidence of cardiovascular events is related to an increase in the AHI at the expense of both obstructive and central

apneas[91]. A meta-analysis concluded that the prevalence of sleep-disordered breathing in patients with acute coronary syndrome was 43% for an AHI >15 and 25% for an AHI >30[92].

1.5.1.4 Arrhythmias

Many studies have found an increased prevalence of atrial fibrillation in patients with sleep-disordered breathing compared to controls or the general population[93,94], some finding up to four-fivefold higher odds of atrial fibrillation in moderate-severe sleep-disordered breathing[94,95]. Increasing severity of sleep-disordered breathing is associated with a progressive increase in odds of atrial fibrillation[96]. Incident atrial fibrillation is also associated with OSA and nocturnal oxygen desaturation[66,97]. Some studies suggest that atrial fibrillation is more strongly associated with central respiratory events than with obstructive events[96]. OSA patients are even at a higher risk of recurrent atrial fibrillation, as shown by a meta-analysis that concluded that the risk of atrial fibrillation recurrence after catheter ablation was 25% higher in OSA patients than in those without OSA[98].

Studies on the association between OSA and ventricular arrhythmias are heterogeneous and scarce, but patients with OSA appeared to have higher odds of ventricular ectopy and arrhythmias, as shown in a systematic review[99].

OSA is a risk factor for sudden death[100,101]. A longitudinal study following 10,701 adults during 15 years showed that OSA predicted incident sudden cardiac death (fatal or resuscitated), and the magnitude of the risk was predicted by multiple parameters related to OSA severity, like AHI and nocturnal oxygen desaturation, even though the magnitude of the risk was much lower than other risk factors (like established coronary disease or heart failure)[100]. Another study that analyzed the risk of malignant cardiac arrhythmias in patients with congestive heart failure after implanting a cardiac resynchronization device with cardioverter-defibrillator found that the time period to first monitored ventricular arrhythmias and to first appropriate cardioverter-defibrillator therapy was significantly shorter in patients with either central sleep apneas or OSA[102].

1.5.1.5 Stroke

Multiple observational studies have found an association between OSA and the risk of stroke, independent of confounders like hypertension or obesity[67,103–106], that is stronger as the severity of OSA increases[104,105]. In a community-based sample of 5422 subjects with OSA, followed for 8.7 years, men with an AHI higher than 19 had an adjusted hazard ratio (HR) of 2.86 for the risk

of ischemic stroke[67]. In another population study of subjects followed for 20 years, moderate-severe OSA showed a HR for incident stroke of 3.7[106]. A recent study concluded that patients with sleep-disordered breathing (SDB) are even at higher risk of recurrent stroke after a first episode[107]. Patients with stroke have a higher prevalence of sleep-disoredered breathing than the general population due either to obstructive or central apneas and hypopneas, but obstructive events are more frequent than the latter[108].

1.5.1.6 Other cardiovascular diseases

It has been estimated that OSA patients have about a 20% prevalence of pulmonary hypertension[109,110]. Generally, the degree of pulmonary hypertension is mild, but some studies have also found severe cases that are associated with functional limitations and a higher mortality in OSA[111]. While some studies found a reduction in pulmonary arterial systolic pressure with CPAP treatment[112,113], the reduction is modest, and its relevance unknown since studies that analyze more relevant outcomes are lacking.

OSA has also been associated with a higher risk of venous thromboembolism. A systematic review found that it is an independent risk factor for either deep-vein thrombosis or pulmonary embolism, and two prospective studies was found that the risk is two- to three-fold higher in patients with OSA than in those without[114].

1.5.1.7 Impact of CPAP treatment

Multiple observational studies have found that CPAP treatment reduces the risk of cardiovascular events, all-cause and cardiovascular mortality in OSA[89,115–117]. However, randomized controlled trials (RCTs), despite showing an improvement in respiratory events, daytime sleepiness, or blood pressure control with CPAP treatment, have failed to show any protective role on cardiovascular events and mortality.

The SAVE (Sleep Apnea Cardiovascular Endpoints) study is one of the largest RCTs performed so far. It randomized 2717 patients with moderate-severe OSA and established coronary or cerebrovascular disease to CPAP treatment plus usual care or usual care alone. They performed a 3.7-year follow-up and found that CPAP treatment was not associated with a significant reduction of cardiovascular events (composite of death from cardiovascular causes, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or transient ischemic attack). AHI was reduced from 29 to 3.7 events per hour. CPAP significantly reduced snoring and daytime

sleepiness, and improved health-related quality of life and mood. It is worth stressing that sleepy patients were excluded from the study, and adherence to CPAP therapy was low (3.3 hours per night)[118]. So far, this is the largest trial of sleep apnea and CV disease but still is one-tenth the size of many primary and secondary multi-national CV disease trials.

The RICCADSA (Randomized Intervention with Continuous Positive Airway Pressure in CAD and OSA) trial performed a randomization of 244 moderate-severe OSA patients with newly revascularized coronary artery disease and without sleepiness (ESS < 10), to auto-titrating continuous positive airway pressure or no positive airway pressure. The primary endpoint was the first event of repeat revascularization, myocardial infarction, stroke, or cardiovascular mortality. Median follow-up was 57 months. The incidence of the primary endpoint did not differ significantly in patients who did versus did not receive continuous positive airway pressure. Adjusted on-treatment analysis showed a significant cardiovascular risk reduction in those who used continuous positive airway pressure for ≥4 vs. <4 h/night or did not receive treatment[119].

The ISAACC study (Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome. Effect of intervention with CPAP) is a multicenter RCT that randomized 1264 patients with moderate-severe OSA that had just been hospitalized for acute coronary syndrome to CPAP plus usual care or usual care alone. The primary outcome was a composite of cardiovascular events (cardiovascular death or non-fatal events (acute myocardial infarction, non-fatal stroke, hospital admission for heart failure, and new hospitalizations for unstable angina or transient ischaemic attack)). Patients with ESS ≥ 10 were excluded. Median follow-up was 3.35 years. The prevalence of cardiovascular events was similar in the CPAP and usual care groups. Adherence was low (2.78 h/night)[119].

Recent meta-analyses of RCTs have not found a reduction of all-cause death or cardiovascular events (including acute coronary syndrome events, stroke, vascular death) with positive airway pressure treatments in OSA[120,121]. These negative results in RCTs are controversial since many of the trials present important biases, like excluding patients with daytime sleepiness or reporting very low adherence to CPAP treatment (below 4hours/night)[122]. Further studies that overcome these biases or better target OSA patients at higher cardiovascular risk are needed to elucidate whether improvement of OSA leads to a reduction of mortality and cardiovascular events.

1.5.2 Metabolic diseases

OSA is associated with an increased risk of developing glucose intolerance, insulin resistance, and type 2 diabetes, regardless of confounding factors like obesity[123–126].

A large European cohort study found that type 2 diabetes prevalence increased with OSA severity, from 6.6% in subjects without OSA to 28.9% in those with severe OSA, despite adjustment for age, obesity, smoking history, comorbidities, and medication prescription. Diabetic subjects with more severe OSA had worse glycemic control than those without sleep-disordered breathing[127].

In diabetic patients, OSA is also significantly associated with diabetes complications like peripheral artery disease, retinopathy, peripheral neuropathy, and diabetic nephropathy[128–131].

Metabolic syndrome is highly prevalent in OSA patients[132]. In patients with metabolic syndrome, OSA is independently associated with increased glucose and triglyceride levels, markers of inflammation, arterial stiffness, and atherosclerosis, supporting the idea that OSA might exacerbate the cardiometabolic risk attributed to obesity and metabolic syndrome[133].

OSA is also associated with a higher risk of developing nonalcoholic fatty liver disease, independent of obesity and other risk factors[134–136]. Different studies have found that this relationship is related to the degree of nocturnal hypoxemia in OSA[137].

Few studies have analyzed the effect of CPAP on metabolic diseases and their complications, with conflicting results. While some meta-analyses have not found a benefit in glucose metabolism in CPAP-treated patients with type-2 diabetes and OSA[138,139], other studies suggest that CPAP might improve insulin resistance in non-diabetics[140] and glucose metabolism in prediabetes OSA patients[141]. A recent retrospective study on 1206 patients, followed for 7.3 years, showed that regular CPAP use was associated with reduced risk of incident type 2 diabetes after adjustment for various baseline metabolic risk factors and subsequent body weight change[142].

1.5.3 Renal disease

Patients with chronic kidney disease have an increased prevalence of obstructive and central sleep apnea[143–146]. A worsening of the kidney function and declination of the glomerular filtration rate is associated with higher OSA prevalence and severity[147]. In patients on hemodialysis, the presence of OSA is associated with an increased risk of cardiovascular events compared to those without OSA[148].

In OSA subjects, longitudinal studies have shown an association with a higher incidence of chronic kidney disease and a faster decline in kidney function over time[149–151]. This finding has

not been universal, as shown in a large 20-year population-based substudy of the Wisconsin cohort[152]. Other studies have found associations between nocturnal hypoxemia and accelerated kidney function loss[153,154]. A cross-sectional study of the ESADA (European Sleep Apnea Database) cohort found that worse nocturnal lowest oxygen saturation was a predictor of chronic kidney disease[155].

Few and small studies have assessed the impact of CPAP treatment on renal function. CPAP treatment could ameliorate glomerular hyperfiltration[156], renal hemodynamics[157], improve estimated glomerular filtration rate values[158] or slow its decline[159]. A meta-analysis performed to determine whether PAP therapy could increase glomerular filtration rate in sleep-disordered breathing patients found negative results; however, subgroup analyses indicated that glomerular filtration rate was significantly increased after PAP treatment in elder patients and patients with a therapeutic duration of at least three months[160]. An RCT performed in patients with moderate-severe OSA and cardiovascular disease could not demonstrate a difference in the rate of estimated glomerular filtration decline between patients treated with CPAP and patients receiving usual care after a 4.4-year follow-up[161].

1.5.4 Respiratory diseases

1.5.4.1 Obesity hypoventilation syndrome (OHS)

Obesity hypoventilation syndrome is defined by the presence of obesity, daytime hypercapnia, and sleep-disordered breathing, in the absence of other causes of hypoventilation (like significant lung or respiratory muscle disease)[162,163]. Severe obesity is a major risk factor for the development of OHS. The estimated prevalence of OHS in patients with suspected OSA and obesity varies between 8 and 20%[164–166]. However, 90% of patients with OHS have OSA, and nearly 70% have severe OSA[167].

Patients with OHS have higher mortality and are at higher risk of cardiovascular events than patients with OSA alone[168]. OHS is also associated with increased rates of pulmonary hypertension, heart failure, and hospitalizations due to acute-on-chronic hypercapnic respiratory failure[169].

Positive airway pressure (CPAP or non-invasive ventilation) improves both sleep-disordered breathing and daytime hypoventilation, being the primary recommended treatment[170].

1.5.4.2 Chronic obstructive pulmonary disease (COPD)

The association between OSA and COPD, classically called "overlap syndrome", can be frequently seen in patients diagnosed with either OSA (7.6 to 55.7%) or COPD (2.9 to 65.9%)[171]. Similar to OSA, COPD is associated with poor sleep quality and hypoventilation during sleep[172,173].

Overlap syndrome patients have been shown to have more significant nocturnal oxygen desaturation and worse sleep quality than patients with only OSA[171]. Some studies have shown that overlap syndrome is associated with higher mortality, more hospitalizations because of COPD exacerbations, and increased risk of cardiovascular events compared to patients with OSA or COPD alone[174–176]. However, a large population study found that a decrease in FEV_1 was associated with increased all-cause mortality of a lower proportion in sleep-disordered breathing subjects compared to subjects without sleep-disordered breathing[177]. It has been proposed that different COPD phenotypes could impact differently on the development of OSA: the increased lung volumes and low BMI associated with the predominant emphysema phenotype could protect against OSA, whereas the peripheral edema and higher BMI often associated with the predominant chronic bronchitis phenotype could promote OSA[178,179]. Few observational studies have evaluated the effect of CPAP treatment in overlap syndrome. Some have reported a protective effect on mortality[176,180,181].

1.5.4.3 Asthma

Asthma patients have a high prevalence of OSA and 2.64 higher odds risk of OSA than non-asthma patients[182]. OSA is more prevalent in patients with severe asthma than moderate asthma[183], is associated with not-well-controlled asthma[184], and with a higher frequency of severe asthma exacerbations[185,186]. Patients with severe asthma have increased AHI, poor sleep quality, and daytime sleepiness[183].

Studies in OSA patients have also shown a relationship with asthma, especially in women[187–189]. In a cohort of subjects referred for suspected OSA, obesity was highly prevalent in asthmatic women, whereas BMI distribution was similar in men with and without asthma[190]. Different mechanisms have been proposed to explain the co-occurrence of OSA and asthma, in addition to shared risk factors like rhinitis, gastroesophageal reflux, and obesity[191]. OSA seems to be related to neutrophilic airway inflammation rather than eosinophilic[192,193]. The effect of CPAP treatment in OSA patients with asthma has been little explored with mixed results. Some studies have found positive results[194–196], while others have not[197,198]. A systematic

review concluded that asthmatics with co-existing OSA can experience improved quality of life with CPAP treatment, especially in severe OSA or poorly controlled asthma[199].

1.5.5 Cancer

Several studies, both population-based and clinical cohorts, have found an increased cancer incidence and mortality in OSA subjects, associated with OSA severity and nocturnal hypoxemia[105,200–203]. However, these findings have not been universal[204,205]. Two meta-analyses have not found an association between OSA and cancer incidence or mortality[206,207]. Experimental research on animal models has shown that intermittent hypoxia, mimicking OSA, increases tumor incidence, malignancy, and mortality, in mice[208].

Some studies have focused on specific cancer localizations, finding an association between OSA and melanoma, pancreatic and kidney cancer, but showing in OSA patients a lower risk of developing colorectal, breast, and prostate cancers compared to non-OSA subjects[209–211]. The association between OSA and malignant melanoma has been investigated with particular interest: OSA and intermittent hypoxia have been linked to increased melanoma growth rate and aggressiveness[212–214].

Further research is needed to confirm the OSA-cancer relationship and evaluate the potential benefit of CPAP treatment.

1.5.6 Neuropsychiatric dysfunction

OSA in middle-aged adults is associated with deficits in multiple cognitive domains such as attention, vigilance, episodic memory, working memory, and executive function[215–217]. Some reports have found an association with a higher risk of developing mild cognitive impairment, dementia, or earlier age of progression to Alzheimer's disease[218,219]. A systematic review and meta-analysis found that adults with OSA were 26% more likely to develop relevant cognitive decline or dementia[220]. However, the evidence linking OSA with cognitive impairments is still weak[221].

OSA is also related to fatigue, irritability, and symptoms of depression. Different studies have found an association of sleep-disordered breathing severity with depression[222–224]. A population-based study found that subjects with OSA had 2.18 times increased risk of subsequent depressive disorder within a year, compared to those without OSA[225]. This association seems to

be stronger in women than in men[62,225]. A randomized controlled trial performed in women with moderate-to-severe OSA found that three months of CPAP therapy improved quality of life, mood state, anxiety and depressive symptoms, and daytime sleepiness, compared to conservative treatment[226].

1.5.7 Other diseases

Although much less studied, there are reports that associate OSA with symptoms or comorbidities related to a variety of fields, such as rheumatological diseases (rheumatoid arthritis[227], gout[228]), ocular manifestations (floppy eyelid syndrome, glaucoma, nonarteritic anterior ischemic optic neuropathy, central serous retinopathy, retinal vein occlusion[229]), sexual dysfunction[230] and Parkinson's disease[231].

1.5.8 Motor vehicle crashes

Sleep fragmentation and daytime sleepiness lead to a higher risk of traffic road accidents in OSA subjects. Motor vehicle crashes are two to three times more common among patients with OSA[232,233]. OSA is also associated with a higher risk of occupational accidents in workers[234]. This is a major problem, particularly in commercial drivers[235].

Evidence indicates that CPAP treatment improves excessive daytime sleepiness (EDS) and reduces the risk of motor vehicle crashes and near-miss accidents[5,236].

1.6 TREATMENT

1.6.1 General considerations

There are different options for treating patients with OSA. They can be grouped or classified as behavioral measures, positive airway pressure devices, oral appliances, surgical procedures, and alternative treatments. Most of them are complementary and not exclusive; thus, they can be offered either singly or in combination according to the patient's characteristics and preferences.

Behavioral measures and lifestyle interventions are recommended to all patients with OSA. These include weight loss, regular aerobic exercise, abstinence from alcohol, and avoiding supine sleep position[26].

Since most OSA patients are overweight or obese, weight loss interventions are an essential pillar in the management of the disease. Several studies have shown that weight loss is associated with an improvement of the AHI[237,238], reducing OSA severity, reversing common comorbidities, and improving quality of life[239]. Greater weight loss is associated with more significant benefits and can be achieved through lifestyle interventions, bariatric surgery, and medications, which all have shown to improve OSA severity[238,240,241].

Exercise is important too: a population study has shown that lack of exercise was associated with increased severity of sleep-disordered breathing[242]. Small randomized controlled trials have shown that performing exercise improves OSA, independently of weight loss[243,244]. Avoiding supine sleep position (sleeping on the side or prone position) is particularly indicated for patients with positional OSA, in whom it could be enough to improve the disease[245].

Positive airway pressure (PAP) is the standard and most effective treatment for OSA. PAP devices deliver pressure through a mask wore over the nose or nose and mouth, splinting the upper airway open and preventing obstructive events during sleep. Strong evidence indicates that PAP significantly reduces disease severity (more than 90% of the patients normalize their AHI), sleepiness, blood pressure, motor vehicle accidents, and improves the sleep-related quality of life in adults with OSA[5,246].

There are different modalities to deliver PAP treatment. CPAP devices deliver a fixed pressure to the airway. Automatic titrating PAP devices are able to sense flow-based changes such as apnea, hypopnea, or inspiratory flow limitation and adjust the pressure in response to changes in the airway flow. Bilevel PAP devices deliver a higher pressure during inspiration and a lower one during expiration. To start PAP therapy, the device needs to be manually or automatically titrated in each patient to establish its therapeutic level. This could be achieved with an

automatic titrating PAP device at home or performing an in-laboratory PAP titration study. Automatic PAP titration reduces costs and allows faster treatment initiation, being as effective as in-laboratory manual titration studies in adult patients without significant comorbidities. In-laboratory titration studies have the advantage of allowing real-time visual identification of the efficacy of therapy and immediate interventions to make PAP treatment more comfortable for the patient[247]. In-laboratory titration is preferred for patients with conditions that determine significant nocturnal hypoxemia, hypoventilation, or central sleep apneas (like chronic heart failure, significant lung diseases, or hypoventilation syndromes)[247]. For ongoing treatment, automatic PAP devices or bilevel PAP devices have not shown significant differences in effectiveness or tolerance compared with standard CPAP[5], although some patients benefit from this treatment modality. As long as factors predicting higher compliance to automatic PAP devices are not found, a trial with automatic devices in patients poorly compliant to fixed CPAP may be warranted. Bilevel devices are useful in conditions that determine hypoventilation.
Patients are advised to use the PAP device every night while they sleep. It has been shown that the more hours per night the PAP device is used, the greater the benefits. A higher adherence is associated with greater improvement in symptoms and blood pressure reductions[79,248,249]. Nonetheless, CPAP adherence is often sub-optimal, especially in patients without excessive daytime sleepiness[250]. The use of educational, behavioral, troubleshooting, and telemonitoring interventions improves PAP adherence[5]. A "good adherence" is considered when a patient uses the device at least 4 hours a night during 70% of the nights[59].

Oral appliances, particularly mandibular advancement devices, are an effective treatment for OSA, especially for mild-moderate cases and those who do not tolerate CPAP[251]. Mandibular advancement devices consist of plates made to fit the upper and lower teeth worn intraorally at night. The adjustment of the position of the plates allows to gradually advance the mandible resulting in an enlarged upper airway and reduced collapsibility[252,253]. Although not as effective as PAP, RCTs have reported a greater than 50% reduction in the AHI with oral appliances (mean reduction of the AHI of 13.6 events/hour compared to control groups), and the adherence rates using oral appliances seem to be greater than the observed with CPAP treatment[254].

Surgical modifications of the upper airway might be indicated for selected patients that are symptomatic and do not tolerate PAP treatment[255]. Most of them modify the upper airway's soft tissue, being the most common the laser-assisted uvulopalatoplasty, the uvulopalatopharyngoplasty, radiofrequency ablation, and palatal implants. Bony structures can also be modified, like in the case of the maxillo-mandibular advancement surgery. The uvulopalatopharyngoplasty is one of the most studied procedures. Two small randomized

trials found a reduction in the AHI of 54-60% in treated patients compared to 11-12% in the control groups[256,257]. A meta-analysis evaluating maxilla-mandibular advancement surgery's outcomes found a mean reduction in the AHI of 80.1%[258]. Still, rigorous data on the effectiveness and the patient-selection criteria for each procedure is limited.

There are alternative treatments for OSA that are reserved for particular OSA phenotypes or are still under investigation. For example, hypoglossal nerve stimulation to increase pharyngeal dilator muscle tone during sleep[259]; pharmacological therapies (atomoxetine, oxybutynin) to increase airway muscle tone, ventilatory drive or raise the arousal threshold[260]; orofacial myofunctional therapy to promote changes in the musculature of the upper airways[261]; nasal expiratory positive airway pressure devices[262]; oral pressure therapy[263].

1.6.2 Treatment indications

The goals of OSA treatment are to resolve the signs and symptoms of the disease, restore quality of sleep, normalize the AHI, improve nocturnal oxygen saturation, reduce the risk of complications and reduce the costs of the disease.

The latest Spanish Respiratory Society of Pulmonology and Thoracic Surgery's international consensus advocates the following therapeutic measures[59]:

- All patients with OSA should be recommended behavioral measures and lifestyle interventions, especially weight loss in those with overweight or obesity.

- Reversible causes of OSA should be evaluated and treated if possible (such as hypothyroidism, tonsillar hypertrophy).

- CPAP treatment is indicated as the primary treatment for patients with moderate or severe disease that present one or more of the following criteria:

  - excessive daytime sleepiness (ESS > 10)
  - impaired sleep-related quality of life (significant snoring, nocturnal choking episodes, insomnia, morning headache, nocturia, deterioration in work or academic performance, social repercussions and / or fatigue during the day)
  - comorbid hypertension (especially resistant hypertension)

- Patients with mild OSA, moderate-severe OSA without the criteria mentioned above, or patients who refuse or do not tolerate CPAP should be individually evaluated and offered oral appliances, positional therapy, surgical or alternative treatments.

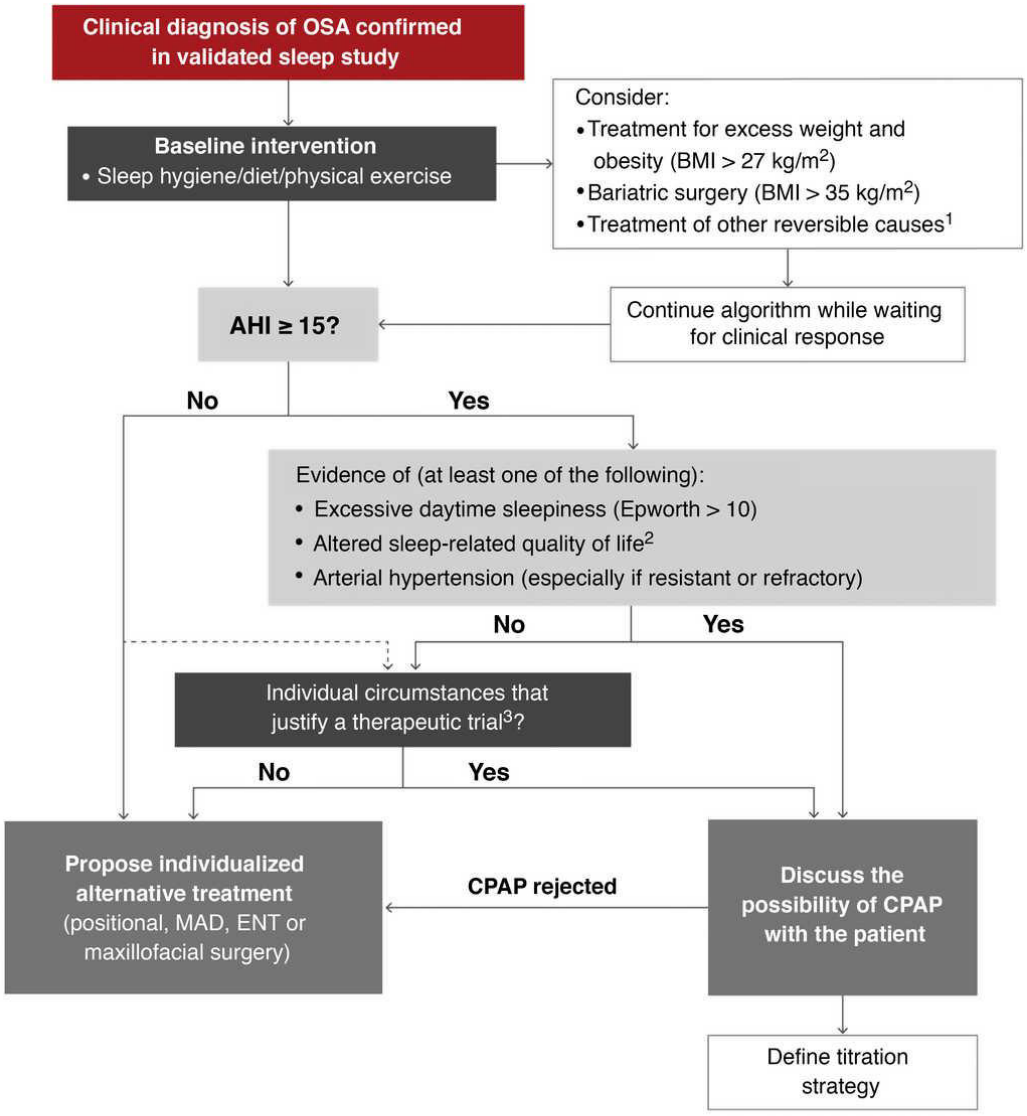
- Patients with mild OSA that are very symptomatic or have a high cardiovascular, cerebrovascular or metabolic comorbidity burden can be exceptionally considered for a therapeutic trial with CPAP.

- Mandibular advancement devices are indicated to OSA patients of any severity that:

  - have an indication for CPAP treatment but do not tolerate or refuse it
  - have a mild or moderate disease without indication for CPAP treatment who present minor symptoms or snoring that are bothersome

The AASM has similar treatment guidelines but recommends PAP treatment (CPAP or automatic PAP) to OSA patients of any severity that present with excessive daytime sleepiness, impaired sleep-related quality of life and / or comorbid hypertension. The AASM considers that there is insufficient and inconclusive evidence to either recommend or withhold PAP to treat non-sleepy adults with OSA as a means to reduce cardiovascular events or mortality[247].
The AASM also recommends oral appliances for patients with OSA who are intolerant of CPAP therapy or patients who request treatment of primary snoring[254].

Figure 3. Proposed therapeutic algorithm for obstructive sleep apnea in Spain. Adapted from Mediano et al.[59]



1. Tonsillar hypertrophy, severe dental or facial alterations, acromegaly, hypothyroidism, and others.
2. Given lack of specific clinical questionnaires, consider intense snoring, choking episodes, insomnia, morning headache, nocturia, deteriorated occupational or academic performance, social impact, and/or tiredness
3. Use CPAP with short-term evaluation of therapeutic efficacy and withdrawal in case of no response

AHI: apnea-hypopnea index; BMI: body mass index; CPAP: continuous positive airway pressure; ENT: ear, nose, and throat; MAD: mandibular advancement devices.

2. STUDY RATIONALE

STUDY RATIONALE

OSA is a heterogenic and multifactorial disease: it is associated with higher mortality and multiple comorbidities (especially cardiovascular diseases), its clinical manifestations are very varied (from poorly symptomatic to excessively sleepy, leading to traffic road accidents), and its physiopathology is complex and still little understood. The gold standard treatment for OSA, PAP, effectively reduces OSA severity; however, it has not been possible to demonstrate a reduction in mortality or cardiovascular events in RCT's. The absence of stratification by other syndrome characteristics other than the AHI might make it more challenging to comprehend the biological basis of the disorder, understand its prognostic implications, and address appropriate diagnostic and treatment decisions, leading to inefficient use of the healthcare system and patient resources. In this context, a need arises for classifying the disorder into smaller, more homogeneous categories: phenotypes.

2.1 Classical phenotyping

Classical methodology for phenotyping was based on hypotheses formulated from observations of a few disease features linked to relevant outcomes. In this way, specific OSA groups have been described, for example:

- OSA in the elderly: in these patients, OSA is less associated with obesity, sleepiness, and loud snoring, while cognitive impairment and nocturia are more frequent than in younger OSA patients[264,265]. It has been observed that the elderly have increased upper airway collapsibility compared to younger patients[266], which is thought to be involved in the increased prevalence of the condition in this age group. Even the association between OSA and comorbidities like hypertension[75] or atrial fibrillation[267] does not seem to be clear in this group. Thus, it has been proposed as a particular OSA phenotype[266].
- EDS-OSA: sleepiness is not a universal finding in OSA. In Spain, Duran et al. described that, in a population-based sample of subjects aged 30 to 70 yr, EDS occurred in 18% of the subjects and was not associated with OSA[8]. Many studies comparing SDB patients with and without EDS have shown that EDS is associated with a higher risk of hypertension, insulin resistance, and mortality[268–271]. Even though CPAP treatment effectively reduces EDS and disease severity[5], different studies show that it produces a more significant reduction in blood pressure[76] and quality of life in patients with EDS[272], compared to non-sleepy patients. Moreover, several studies have not found a beneficial effect of CPAP on hypertension[80–82]

or cardiovascular risk[273,274] in non-EDS OSA. EDS-OSA could be considered a special OSA phenotype since this group is associated with higher comorbidity risk and better response to CPAP treatment[275], even though these findings have not been universal.

- Nocturia and nighttime hypertension are common in patients with OSA and share several physiopathological pathways[276,277]. A recent study from our team has found that the presence of nocturia in severe OSA patients with nighttime hypoxemia increases the probability of nighttime hypertension and of non-dipping pattern[278]. The presence of nocturia could represent an OSA phenotype at increased cardiovascular risk.
- REM-OSA: refers to subjects who have more severe OSA during rapid eye movement (REM) sleep than during non-REM sleep, or exclusively during this sleep stage, although there is no consensus on the criteria to define it. REM sleep is associated with greater sympathetic activity, lower vagal tone, and more cardiovascular instability than non-REM sleep[279]. Evidence indicates that REM-OSA is independently associated with adverse cardiovascular, metabolic, and neurocognitive outcomes[280]. It has been proposed that CPAP treatment might fail to reduce the comorbidity risk associated with OSA because a mean use of 3-4 hours a night would leave 75-60% of obstructive events during REM sleep untreated[280], as the duration of this sleep stage increases in the last part of the night.
- Multiple-feature phenotyping: Eckert et al. performed a study analyzing physiological traits of OSA, developing a scale to categorize patients according to passive critical closing pressure of the upper airway, arousal threshold, loop gain, and the muscle responsiveness (the "PALM" scale)[281]. Afterward, they incorporated the physiological traits into a model to predict OSA. They analyzed the effect of various trait manipulations to treat OSA, finding that their model had good sensitivity and specificity to predict OSA and that combination therapy with two interventions (to modify the traits) was predicted to treat OSA in approximately 50% of patients[282]. This is a good example of phenotyping patients according to various characteristics and relating them to clinical outcomes.

2.2 New ways of phenotyping: cluster analysis

In the past decade, computer science has enabled the development of unsupervised learning methods that have allowed phenotyping in a completely different way, analyzing multiple variables at the same time and discovering links and associations not readily apparent among them. Unsupervised learning is a methodology in which computer algorithms are not provided with pre-assigned labels or scores for the training data. Unsupervised learning algorithms must

first self-discover any naturally occurring patterns in that training data set. Examples of these statistical technics include cluster analysis, anomaly detection, neural networks and latent variable models.

Cluster analyses consist of grouping a set of objects in such a way that objects in the same group (called a cluster) are more similar to each other than to those in other groups (other clusters).

Unlike classical phenotyping that is hypothesis-driven (or supervised), these are hypothesis-generating approaches that focus on discovering emerging patterns within the data by grouping subjects into homogeneous categories on the basis of unique associations between subject features[283]. Using different variables (e.g., polysomnographic features, symptoms, comorbidities), subjects are grouped into different clusters where members of each cluster are as similar as possible to each other and as different as possible from those in other clusters[284]. There are many statistical methods for clustering, such as latent class analysis, K-means clustering, principal component analysis, hierarchical cluster analysis and Partition Around Medoids (PAM).

2.3 Cluster analyses in OSA

Cluster analyses provide a multiple-feature assessment, optimal for better tackling OSA's complexity. In recent years, many studies have emerged using this new approach. Different statistical methods for clustering have been used and different variables for cluster definition. As a result, a large number of distinctive OSA phenotypes have been described that seem difficult to compare across studies (Table 1) .

Table 1. Summary of the most relevant cluster analyses performed in OSA using multiple domains for classification.

Study (year)	Sample	Methodology	Variables used for clustering	Identified phenotypes		Clinical characteristics and outcomes
Joosten et al. (2012)[285]	Clinical n=1,184 Mild-moderate OSA	PSG phenotypes + validation through K-means clustering	Demographics Anthropometrics ESS PSG data	1. Supine predominant-OSA (clusters 1 and 2)		Younger, lower BMI, sleepier
				2. Supine isolated OSA (cluster 3)		
				3. REM predominant OSA (cluster 4)		44% of females
				4. REM isolated OSA (no cluster identified)		
				5. REM-supine overlapping OSA (clusters 6 and 5)		
				6. NREM predominant OSA (no cluster identified)		
				7. Intermittent OSA (no cluster identified)		
Ye et al. (2014)[286]	Clinical (Iceland, ISAC cohort) n=822 Moderate-severe OSA	Latent class analysis	Symptoms ESS Comorbidities (hypertension, diabetes, cardiovascular disease, obstructive lung disease)	1. Disturbed sleep (32.7%) – insomnia-related symptoms, 21.6% females		Highest use of hypnotics
				2. Minimally symptomatic (24.7%)		Highest probability of comorbidities (hypertension, diabetes, and cardiovascular disease)
				3. Excessive daytime sleepiness (42.6%)		Lowest probability of comorbidities
Babbin et al. (2015)[287]	Clinical n=161 AHI ≥ 5	Time series analysis and dynamic cluster analysis	Hours per day of CPAP use over 180 days	1. Great users (17%)		Good users reported more vigilance (FOSQ) than low users and slow decliners. Good users reported higher productivity (FOSQ) than low and great users. Great and good users had higher sleep quality than low users.
				2. Good users (33%)		
				3. Low users (23%)		
				4. Slow decliners (27%)		
Vavougios et al. (2016)[288]	Clinical n=1,472 Suspected OSA	Categorical principal component analysis and two-steps clustering	Comorbidities of the Charlson Index AHI	A: Healthy	(cluster 3) no OSA, with sleep-related disturbances and moderate somnolence	Older age, greater BMI, lower daytime oxygen saturation and hypertension were associated independently with an increased risk of belonging in a comorbid cluster.
				B: Mild OSA	(cluster 1) mild OSA without comorbidities but higher prevalence of coronary artery disease compared to phenotype A	
				C: Moderate OSA	- C1 (cluster 6): without comorbidities but obesity. - C2 (cluster 2): with severe comorbidities, obesity and stroke.	
				D: Severe OSA + obesity	- D1 (cluster 4): without comorbidities and a 33.8% prevalence of hypertension. - D2 (cluster 5): with severe comorbidities, highest ESS and highest BMI.	

Gagnadoux et al. (2016)[289]	Clinical n=5,983 Moderate-severe OSA	Latent class analysis Follow-up of CPAP use	Demographic Anthropometric Symptoms (sleep-related, insomnia, depression, EDS) Comorbidities (hypertension, diabetes, cardiovascular disease)	1. "Female OSA" (14%): 90.2% females, high rates of insomnia complaints, depressive symptoms, obesity, and associated comorbidities	CPAP treatment success at 6 months: lower rates of success in the "female", "mildly symptomatic" and "comorbid OSA" phenotypes than in the "severe OSA syndrome" phenotype.
				2. (15%) Typical nocturnal and diurnal OSA symptoms, frequent depressive symptoms. Compared to cluster 1: male predominance and more frequent comorbidities	
				3. "Severe OSA syndrome" (18%): nocturnal and diurnal OSA symptoms, frequent depressive symptoms, youngest, no comorbidities	
				4. "Mildly symptomatic"(32%): nocturnal OSA symptoms, insomnia complaints, low prevalence of EDS, depressive symptoms, and minimal comorbidities	
				5. "Comorbid OSA" (21%): minimally symptomatic male patients, older than 65 years, high rate of comorbidities	
Bailly et al. (2016)[290]	Clinical n=18,263 AHI >15 or ODI >15	Ascending hierarchical cluster analysis	Demographic Anthropometric Symptoms Comorbidities (hypertension, diabetes, cardiovascular disease, and others)	1. Young, overweight, symptomatic OSA without comorbidities: the young symptomatic (10%).	Highest ESS and near-miss road accidents
				2. Elderly, minimally symptomatic, obese, OSA with few comorbidities: the older obese (23%).	
				3. Elderly, minimally symptomatic, multimorbid OSA: the multi-disease old obese (19%).	Highest proportion of cardiovascular and respiratory disease, along with cluster 6
				4. Young, overweight, minimally symptomatic OSAS without comorbidities: the young snorers (15%).	
				5. Middle age, with few symptoms of OSA but ESS, and few comorbidities: the drowsy obese (19%).	
				6. Middle age, symptomatic multimorbid OSA with particularly poor lifestyle habits: the multi-disease obese symptomatic (15%).	More frequently complained of nocturia. Highest proportion of cardiovascular and metabolic disease, along with cluster 3
Lacedonia et al. (2016)[291]	Clinical n=198 AHI ≥ 5 Excluded patients with COPD, OHS, neuromuscular disease, and central apnea	Principal component analysis, network analysis with hierarchial and local optimizing clustering	Demographic Anthropometric Cardiorespiratory polygraphy ESS Spirometry Arterial blood gases Comorbidities (cardiovascular and endocrinal disease, hypertension, diabetes, asthma)	1. Younger, very severe OSA, morbid obesity, high T90%, low PaO_2, high prevalence of comorbidities	In cluster 1, PaO_2 is related inversely strictly to BMI and T90%
				2. Moderate-severe OSA, low T90%	
				3. Older, very severe OSA, mild obesity or overweight, low T90%, less sleepy.	

Turinoet al. (2017)[292]	Clinical n=71,217 CPAP-treated patients in Catalonia between 2012 and 2013	Multiple correspondence analysis and k-means clustering	Demographics Comorbidities (30 conditions) Mortality Use of healthcare resources	1. Neoplastic (10%): higher prevalence of malignant neoplasm - most frequently genitourinary of gastrointestinal origin - high mortality. 2. Metabolic syndrome (28%): low mortality 3. Asthmatic (6%): high proportion of women (53%) and low mortality 4. Musculoskeletal and joint disorders (10%): 36.2% females, lowest mortality 5. Patients with few comorbidities (35%) 6. Oldest and cardiac disease (10%): median age 72, highest mortality rates	Cohort characterized by middle-aged men with a high prevalence of hypertension, dyslipidemia, diabetes, and obesity. Clusters 1 and 6 showed the highest mortality and rate of hospitalization, almost certainly due to underlying comorbidities rather than as a result of OSA.
Zinchuk et al. (2018)[293]	Clinical n=1,247 U.S. Veterans suspected of OSA	Principal components analysis and K-means clustering Longitudinal analysis of 1º outcome and CPAP use at 4.9 years 1º Outcome: composite of incident transient ischemic attack, stroke, acute coronary syndrome, or death	65 PSG variables	1. Mild (43%): median AHI 4 2. PLMS (20%): median AHI 10, older, higher PLMS index, higher T90%, and higher comorbidity than the "mild" cluster 3. NREM and poor sleep (15%): median AHI 19, NREM apneas and hypopneas, spontaneous arousals, low sleep efficiency 4. REM and hypoxia (15%): median AHI 19, highest REM apneas, increased T90% (9%) 5. Hypopnea and hypoxia (6%): median AHI 44, hypopneas with desaturation and high T90% (14%) 6. Arousal and poor sleep (3%): median AHI 68, apneas with arousals without desaturations, disturbed sleep architecture, low T90% (4%), older and lower CPAP use. Highest percentage of Black and Hispanic patients. 7. Combined severe (10%): median AHI 84, combined apneas with arousals and desaturation, highest T90% (20%), high percentage of stage I sleep	The PLMS cluster exhibited a greater than twofold higher risk of primary outcome compared to the mild cluster. After adjustment with Framingham risk score, age, sex, and baseline cardiovascular risk, the association with the risk of the primary outcome remained significantly increased for the PLMS, hypopnea and hypoxia, and combined severe clusters. Conventional OSA categories based on AHI were not associated with the primary outcome. The REM and hypoxia cluster did not exhibit a statistically higher risk of the primary outcome. Regular CPAP use was associated with a 36% decreased risk of the primary outcome.
Kim et al. (2018)[294]	Population n=422 Moderate-severe OSA	Latent class analysis	Symptoms ESS Comorbidities (hypertension, diabetes, cardiovascular disease)	1. Disturbed sleep (14.5%): insomnia-related symptoms and highest ESS, 52.5% females 2. Minimally symptomatic (55.7%) 3. Excessive daytime sleepiness (29.9%): highest rates of most sleepiness measures, but ESS	They were able to identify three clusters similar to the ISAC study groups. Compared to ISAC: - Older sample, with lower AHI and BMI. - Lower symptom burden and Epworth (5.0 vs. 7.0 in ISAC): the minimally symptomatic was the largest group. The disturbed sleep group had significantly higher rates of hypertension.
Keenan et al. (2018)[295]	Clinical n=972 Moderate-severe OSA (215 from Iceland, 757 from 5 different countries)	Latent class analysis	Symptoms ESS Comorbidities (hypertension, diabetes, cardiovascular disease)	Iceland patients: 1. Disturbed sleep (19.8%): 36.7% females 2. Minimally symptomatic (40.4%) 3. Excessively sleepy (39.8%)	Three similar clusters to the ISAC study groups. None of the clusters had a significantly higher prevalence of comorbidities.
				Outside of Iceland patients: 1. Disturbed sleep (19%): 43.1% females 2. Minimally symptomatic (20.3%) 3. Upper airway symptoms with sleepiness (21.7%): highest ESS 4. Upper airway symptoms dominant (19.4%) 5. Sleepiness dominant (19.6%)	Greater than 80% of the individuals in the 5-cluster solution came from a similar cluster of the 3-cluster ISAC design. There were significant differences in age, gender, BMI, and ethnicity among the five clusters. The disturbed sleep was the cluster with the highest prevalence of comorbidities (and oldest age), while the one with the lowest was the upper airway symptom dominant group (and youngest).
Ferreira-Santos et al. (2018)[296]	Clinical n=211 AHI cutoff not defined (excluded: severe lung diseases and neurological conditions)	K-modes categorical clustering	Demographic Anthropometric Symptoms Comorbidities (heart failure, arrhythmias, pulmonary hypertension)	1. Nonobese, young, drowsy (55%) 2. Female, poor sleep (20%): with headaches and nonrestorative sleep 3. Obese, older, non-drowsy (25%): highest Mallampati score and neck circumference	No outcomes reported. No difference in the AHI or comorbidities among clusters.

Quan et al. (2018)[297]	Clinical n=2,649 ODI4 ≥ 12, with coronary artery (CAD) or cerebrovascular disease (CeVD)	Latent class analysis Randomized to CPAP or usual care: follow up at 3.7 years 1º Outcome: composite of death from CVD, myocardial infarction, stroke or hospitalization for unstable angina, heart failure, or transient ischemic attack. 2º Outcome: stroke	Demographic Anthropometric AHI, T90%, ESS, blood pressure, health habits, comorbidities, medications (antihypertensive, lipid-lowering, antidiabetic, anticoagulation)	1. CeVD + DM (9%) 2. CAD + DM (15%) 3. CeVD (37%) 4. CAD (39%)	CeVD groups were predominantly Asian and more often women. CAD and CAD + DM groups more frequently reported obesity and CV medication. More patients in the CeVD groups had severe OSA compared to CAD groups. CAD and CeVD with DM were at significantly higher risk of recurrent composite CV events and stroke, respectively, compared to individuals without DM. CPAP use > 4h/night reduces the risk of the primary outcome in the CeVD + DM phenotype.
Nakayama et al.(2019)[298]	Clinical n=210 Men, moderate-severe OSA (without PLM>15/h, cardiovascular or psychiatric disease)	Hierarchical cluster analysis	PSG data	1. High fraction of apnea and severe desaturation 2. High fraction of apnea and long event duration 3. Low fraction of apnea	No association with clinical outcomes.
Mazzotti et al. (2019)[299]	Population (Sleep Heart Health Study) n=1,207 Moderate-severe OSA	Latent class analysis Follow up 11.8 years: prevalence and incidence of: 1º Outcome: cardiovascular disease 2º Outcomes: - Coronary heart disease - Heart failure - Stroke - Cardiovascular mortality	Symptoms ESS	1. Disturbed sleep (12%): 45.6% females 2. Minimally symptomatic (33%) 3. Excessively sleepy (17%) 4. Moderately sleepy (39%)	Although no significant associations with prevalent cardiovascular disease were found, the excessively sleepy cluster was associated with more than a threefold increased risk of prevalent heart failure. Symptom subtype was also associated with incident cardiovascular disease, coronary heart disease, and heart failure, with the excessively sleepy again demonstrating increased risk compared with other subtypes.
Schütz et al. (2019)[300]	Clinical n= 451 REI ≥ 10 ≥ 45 years old with stroke in the last 45 days Excluded: patients on supplemental oxygen, mechanical ventilation or PAP therapy, or pregnant.	Latent class analysis	Demographics REI Symptoms Comorbidities National Institute of Health Stroke Scale (NIHSS)	1. Severe strokes (12%): mean age 70.6, mean NIHSS score of 15.6 mean REI 21.1 2. Younger patients with mild strokes and relatively mild OSA (56%): mean age 65.1, mean NIHSS 2.9, mean REI 18.5 3. Severe OSA with a high prevalence of comorbidities (32%): mean age 69.2, mean NIHSS 4.8, mean REI 45.1.	The severe OSA with a high prevalence of comorbidities cluster showed a significantly higher prevalence of coronary artery disease.
Hyun-Joon et al. (2020)[301]	Clinical n= 89 AHI ≥ 5 with EDS or AHI ≥ 15 Exclusion criteria: central sleep apnoea; serious	K-means clustering	AHI BMI 2 cephalometric variables (ANB degree and mandibular plane angle degree)	1. Obesity type (49.4%): moderate OSA, obesity, normal sagittal and vertical skeletal pattern without significant upper airway abnormality 2. Skeletal type (33.7%): moderate OSA, without obesity, severe skeletal Class II hyperdivergent pattern with narrow pharyngeal airway spaces 3. Complex type (16.8%): severe OSA, obesity, skeletal Class II hyperdivergent pattern with posteriorly displaced hyoid and retroclined soft palate	The main contributing factors to AHI were obesity in cluster 1, hyperdivergent vertical pattern with narrow pharyngeal space in cluster 2, and hyperdivergent pattern, obesity, displaced hyoid, and soft palate in cluster 3.

	comorbidities, syndromic craniofacial anomalies, history of upper airway soft tissue or skeletal surgery, history of orthodontic treatment.				
Kim et al. (2020)[302]	Clinical n=4,603 Suspected OSA	Principal component analysis and K-means clustering Follow-up 53.5 months: mortality	29 PSG variables	1. Normal to mild OSA with spontaneous arousal (55.7%): mean AHI 8.52 2. Normal to mild OSA with poor sleep and PLMs (7.6%): mean AHI 12.1, oldest (mean age 63.9), lowest ESS 3. Moderate to severe OSA wih hypopnea (27.8%): mean AHI 38.6 4. Severe OSA with hypoxemia (8.9%): mean AHI 69.6, youngest (mean age 48.2), highest ESS, highest BMI (mean 28.9)	Cluster 4 tended to have the highest prevalence of hypertension, diabetes and smoking. Cluster 4 had a significantly higher risk of cardiovascular/cerebrovascular-related mortality and all-cause mortality compared to cluster 1.
Labarca et al. (2020)[303]	Clinical n=889 Moderate-severe OSA Excluded: respiratory conditions	Latent class analysis Follow-up 4.7 years: 1º Outcome: all-cause mortality 2º Outcome: - cardiovascular mortality - cancer mortality	Four hypoxemic variables from home sleep apnea test (ODI3, T90%, mean and minimal oxygen saturation)	1. Nonhypoxemic (59%) 2. Moderately hypoxemic (28%) 3. Severely hypoxemic (13%): oldest cluster (mean age 61.3), highest ESS, higher rates of hypertension, diabetes and dyslipidemia.	The hypoxemic groups showed an increased risk of all-cause mortality. The risk of cardiovascular mortality was associated with age, diabetes, and coronary heart disease. The risk of cancer mortality was associated with age and severe hypoxemia
Romero-Peralta et al. (2021)[304]	Clinical n=2,025 AHI ≥ 5	Hierarchical cluster analysis	Demographic Anthropometric AHI Symptoms, ESS Comorbidities (hypertension, diabetes, dyslipidemia)	1. Young male without comorbidity with moderate apnea and otorhinolaryngological malformations (32.7%): mean age 42, mean AHI 19 2. Middle-aged male with very severe OSA with comorbidity without cardiovascular disease (10%) mean age 53, mean AHI 81 3. Female with mood disorder (22.5%): mean age 60, 48% female, mean AHI 16.5. Only cluster without obesity (mean BMI 23.8) 4. Symptomatic male with established cardiovascular disease and severe OSA (16.4%): mean age 59, mean AHI 49.3	 Cardiovascular risk factors High rates of depression and anxiety, as well as related medications. Cardiovascular disease

AHI: apnea-hypopnea index; BMI: body-mass index; CAD: coronary artery disease; CeVD: cerebrovascular disease; COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; DM: diabetes mellitus; EDS: excessive daytime sleepiness; ESS: Epworth sleepiness score; FOSQ: Functional Outcomes of Sleep Questionnaire; ISAC: Icelandic Sleep Apnea Cohort; NIHSS: National Institute of Health Stroke Scale; NREM: non-rapid eye movement; ODI: oxygen desaturation index; OHS: obesity-hypoventilation syndrome; OSA: obstructive sleep apnea; PaO2: diurnal partial pressure of oxygen; PLMS: periodic limb movements of sleep; PSG: polysomnography; REI: respiratory event index; REM: rapid eye movement; T90%: percentage of time with oxygen saturation below 90%.

Most studies use PSG variables, symptoms, or comorbidities for cluster definition. Chronic medication is a feature that has not been considered for clustering, excluding data that might provide valuable real-life information that enhances the one available in medical records.

Some of the most studied OSA phenotypes are symptom-based clusters. Ye et al. performed a study in 822 patients with moderate-severe OSA of a clinical cohort of Iceland (ISAC: the Icelandic Sleep Apnea Cohort)[286]. They used 23 variables for cluster analysis that included symptoms, ESS, and four comorbidities (hypertension, diabetes, cardiovascular disease, and obstructive lung disease) and performed a latent class analysis. They were able to identify three clusters: the disturbed sleep group (32.7%) that had insomnia-related symptoms, the minimally symptomatic group (24.7%), and the excessive daytime sleepiness group (42.6%) that was characterized by having classic OSA symptoms. There was no statistical difference in sex, BMI, AHI, ODI, or minimum oxygen saturation among the three clusters. The probabilities of having comorbid hypertension, diabetes, and cardiovascular disease were highest in the minimally symptomatic group and lowest in the excessive daytime sleepiness group. The findings of this study are interesting, not only because they were able to identify different patterns of clinical presentation, but also it is noteworthy that a majority of patients (57.4%) did not express the typical OSA symptoms and that the AHI or ODI was not associated with the symptom subtype or comorbid conditions.

Kim et al. applied the same criteria for cluster analysis as the ISAC study in a population cohort of Korea[294]. They performed a latent class analysis in 422 subjects with moderate-severe OSA using symptoms and three comorbidities (hypertension, diabetes, and cardiovascular disease) for clustering. They were able to identify three subtypes also defined as disturbed sleep, minimally symptomatic and excessively sleepy. Unlike the ISAC study, the most prevalent cluster was the minimally symptomatic group (55.7%); the disturbed sleep group (which had insomnia symptoms) was significantly older and had a higher proportion of women compared to the other clusters, and was the only one significantly associated with hypertension.

Keenan et al. also performed the same cluster analysis as the ISAC study but in an Icelandic cohort and in an international multiethnic cohort[295]. In the latter, they identified three similar clusters to the ISAC study (where 80% of the subjects belonged) and two additional ones, finding that the cluster with the highest prevalence of comorbidities was the disturbed sleep group.

Finally, Mazzotti et al. performed a similar analysis in subjects from the population-based Sleep Heart Health Study, adding a longitudinal analysis to study the association of the clusters with prevalent and incident cardiovascular disease or death[299]. In this case, they found three similar

symptom subtypes plus an additional one. The excessively sleepy cluster was significantly associated with an increased risk of prevalent and incident heart failure, as well as incident cardiovascular and coronary heart disease, compared to the other clusters.

While recognizing the same symptom subtypes of OSA subjects in different cohorts is important as it validates the identified phenotypes, the discordant results in these studies regarding the clusters' relationship to comorbidities raise concerns about its clinical relevance[305]. So far, identifying common subgroups of patients from cluster analyses that lead to worse clinical outcomes has not been possible, representing a field for continuous research.

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 CPAP treatment outcomes[289,293,297,299,306]. Other aspects like the incidence of comorbidities (other than cardiovascular diseases), hospitalizations, or medicine consumption have not been taken into account. 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.

The current research is meant to describe OSA phenotypes performing cluster analysis, using a more comprehensive range of OSA features and patients' clinical data, and to analyze their evolution over time regarding clinical outcomes and treatment decisions.

3. HYPOTHESES

HYPOTHESES

The hypotheses of this research are:

1. It is possible to identify specific OSA phenotypes based on a large number of clinical variables and OSA severity measures.

2. The phenotypes will maintain their defining characteristics in the long term.

3. CPAP treatment will impact outcomes differently in each phenotype.

4. OBJECTIVES

OBJECTIVES

4.1 Primary objective

1. To perform a new cluster analysis aimed to identify relevant OSA phenotypes using clinical, anthropometric, comorbidities, polysomnographic, and chronic medicine prescription information.

4.2 Secondary objectives

2. To validate the identified clusters performing a 5-year follow-up, analyzing the incidence of comorbidities, prescription of chronic medication, hospital admissions, and mortality.

3. To assess the influence of CPAP treatment on incident comorbidities, hospital admissions, and mortality risk in the different clusters.

5. METHODOLOGY

METHODOLOGY

5.1 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 participants). 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.

5.2 Sleep studies

Patients were diagnosed using a home-based respiratory polygraphy or a sleep laboratory-based polysomnography. Home sleep studies (Somnea Compumedics, Abbotsford, Australia) registered oronasal airflow by nasal cannula, respiratory effort by thoracic and abdominal inductive bands, arterial oxygen saturation, heart rate by finger probe, and body position. Conventional nocturnal polysomnography recordings (Profusion E Series, Compumedics, Abbotsford, Victoria, Australia) included electroencephalography, electrooculography, submental electromyography, anterior tibialis electromyogram, oronasal airflow (nasal cannula and oral thermistor), respiratory effort (inductive thoracic and abdominal bands), electrocardiography and body position. Sleep studies were evaluated according to the 2007 AASM Manual for the Scoring of Sleep and Associated Events[307]. Hyopopneas were scored according to the manual's alternative definition: a 50 % or more reduction in nasal pressure signal associated with ≥3% desaturation or arousal. The severity of OSA has been defined as mild (AHI ≥ 5 and < 15), moderate (AHI ≥ 15 and < 30), or severe (AHI ≥ 30).

5.3 Clinical variables and treatment data

Comorbidities and medicine prescriptions were obtained from the Agency for Health Quality and Assessment of Catalonia (AQuAS). 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 Classification of Disease version for 2010 (ICD-10)[308]. Of all the comorbidities recorded, we selected for our dataset the most relevant ones, according to the investigators' criteria. 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[309]. We considered only chronic prescriptions, defined as those medications used for at least four months a year. The drugs included were: beta blockers, calcium blockers, angiotensin-converting enzyme inhibitors, diuretics, antihypertensives, lipid-lowering agents, oral hypoglycemic agents, insulins, antiarrhythmics, antiplatelets, anticoagulants, vasodilators for cardiac diseases, bronchodilators, nonsteroidal anti-inflammatory drugs, corticosteroids, weak and strong opioids, anxiolytics, antidepressants, and hypnotics and sedatives. To ensure the accuracy of the diagnosis of type 2 diabetes mellitus, hypertension and dyslipidemia, new records were generated in the comorbidities dataset, from data of medicine prescription, taking into account the following relationships: for patients who had prescribed "insulins" or "oral hypoglicemic agents" a registry was created in the comorbidities data set with an identification equal to comorbidity "type 2 diabetes mellitus". The same procedure was applied for patients with regular prescription of antihypertensives and the diagnosis of "Hypertension" and for lipid lowering agents and the diagnosis of "Dyslipidemia".

Baseline information on anthropometric data and assessment of daytime somnolence by the ESS was collected from the hospital's medical records.

We also obtained from the AQuAS 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".

For follow-up, the incidence of comorbidities was completed with information on the cause of hospitalization, cause of death, and reason for medical procedure, registering "ischaemic heart disease" when a participant had undergone a coronary revascularization procedure and "chronic kidney disease" when a participant had undergone hemodialysis.

CPAP treatment was prescribed according to the Spanish Respiratory Society of Pulmonology and Thoracic Surgery's guidelines on the diagnosis and treatment of OSA. At that time, CPAP was prescribed to patients with mild or moderate OSA with excessive daytime sleepiness or cardiovascular disease, depending on the physician's criteria, and to severe patients with OSA, regardless of symptomatology[310]. 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" subjects were considered when CPAP was not prescribed or was prescribed but later discontinued.

5.4 Baseline dataset for cluster analysis

The final dataset of variables used for clustering included baseline anthropometric data (sex, age, and body mass index, polysomnography/respiratory polygraphy data (AHI, baseline, mean and minimum oxygen saturation, percentage of time with SaO_2 below 90% (T90%), oxygen desaturation index (ODI) >3% and ODI >4%, ESS, comorbidities and chronic medicine consumption.

5.5 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 versus No CPAP participants.

5.6 Statistical and cluster analysis

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

For variables with missing data, the values were imputed using the MICE method (Multivariate Imputation by Chained Equations), by replacing missing values with 'most likely values' estimated by inference from the rest of the data in the set. 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. In this way, almost the same information is available from a smaller number of variables.

A principal component analysis, Factorial Analysis for Mixed Data (FAMD), has been carried out, which allows balancing the influence of continuous and categorical variables. This method allows studying the similarities between individuals taking into account mixed variables, and studying the relationships between them. It is usual, in this type of analysis, to select those

components that return a high percentage of the information. In this case, all those that returned 90% of the information were selected, which returned a total of 30 dimensions.

A cluster analysis was performed using the components obtained as described. The Euclidean distance was calculated, specifically for quantitative variables. Once the distance matrix was obtained, we calculated the groups from the PAM method (Partition Around Medoids). There are many techniques for creating clusters using unsupervised learning. The PAM method allows the partitioning of groups, minimizing the distance between the individuals of the same group. It is more suitable when the data set has outliers or noise, as is the case. Using FAMD and thanks to the PAM technique that is not affected by collinearity, it was not necessary to eliminate variables that could generate a bias in the clustering model (e.g., depression and antidepressant therapy, dyslipidemia and lipid-lowering agents).

There are a variety of methods for choosing the number of optimal groups to use for cluster analysis. In this case, the silhouette width was used, a metric of internal validation that is an aggregate measure of how similar an observation is to its own conglomerate compared to its closest neighboring conglomerate. This metric can vary from -1 to 1, where higher values are better.

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 (CI) were calculated. For continuous variables, mean (standard deviation), the 95% confidence interval for the mean, and the median and the interquartile range were calculated. In order to compare the different categories, a comparison test between groups was carried out; for quantitative variables, an ANOVA or a Kruskal-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[311], which corrects the p-value by correcting the probability of obtaining a false-positive. For all analyses, a p-value of less than 0.05 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 (2019-12-12), Copyright (C) 2015 (The R Foundation for Statistical Computing).

6. RESULTS

RESULTS

6.1 Cohort's characteristics

During 2014, 1217 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 (SD) 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 (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 2. Information on the prevalence of comorbidities and medicine prescription in the whole cohort is detailed in Table 3. Information of chronic medication showed a much higher prescription of antidepressants, anxiolytics, and hypnotics and sedatives (26.13%, 19.06%, and 4.44%, respectively) than the 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%).

Table 2. Cohort general characteristics and sleep studies data

Variables	n = 1217	
Age (years)	58.1 (13) [57.3;58.8]	
Sex		
Women	348 (28.6%)	
Men	869 (71.4%)	
BMI (Kg/m^2)	30.7 (5.4) [30.4;31]	
ESS	7.2 (4.4) [6.9;7.4]	
AHI	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]	
T90%	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). BMI, body mass index; ESS, Epworth sleepiness scale; AHI, apnea-hypopnea index; OSA, obstructive sleep apnea; SaO_2, oxygen saturation; T90, time percentage with SaO_2 < 90%; ODI, oxygen desaturation index.

Table 3. Comorbidities and medicine prescriptions of the entire cohort

Comorbidities		Medicine Prescription	
Dyslipidemia	619 (50.86%)	ACE inhibitors	513 (42.15%)
Hypertension	570 (46.84%)	NSAIDs	449 (36.89%)
Type 2 diabetes mellitus	241 (19.80%)	Lipid lowering agents	440 (36.15%)
Tobacco use (active or past consumption)	239 (19.64%)	Antidepressants	318 (26.13%)
Depressive disorder	110 (9.04%)	Diuretics	283 (23.25%)
Ischemic heart disease	90 (7.40%)	Antiplatelets	253 (20.79%)
COPD	82 (6.74%)	Anxiolytics	232 (19.06%)
Asthma	68 (5.59%)	Bronchodilators	222 (18.24%)
Solid neoplasms	58 (4.77%)	Beta blockers	195 (16.02%)
Atrial fibrillation	55 (4.52%)	Calcium blockers	193 (15.86%)

Chronic kidney disease	46 (3.78%)	Oral hypoglycemic agents	178 (14.63%)
Heart failure	44 (3.62%)	Weak opioids	93 (7.64%)
Alcohol use disorder	44 (3.62%)	Anticoagulants	84 (6.90%)
Gastroduodenal ulcer	39 (3.20%)	Insulins	69 (5.67%)
Cerebrovascular disease	32 (2.63%)	Antihypertensives	62 (5.09%)
Liver pathology	29 (2.38%)	Corticosteroids	57 (4.68%)
Hypothyroidism	20 (1.64%)	Hypnotics and sedatives	54 (4.44%)
Peripheral vascular disease	19 (1.56%)	Antiarrhythmics	49 (4.03%)
Connective tissue disease	13 (1.07%)	Vasodilators for cardiac diseases	48 (3.94%)
Skin neoplasms	11 (0.90%)	Strong opioids	20 (1.64%)
Insomnia	9 (0.74%)		
Dementia	9 (0.74%)		
Aortic aneurysm	6 (0.49%)		
Hyperthyroidism	5 (0.41%)		
Hematologic malignancies	4 (0.33%)		
AIDS	1 (0.08%)		

Data are shown as frequency (percentage). ACE: angiotensin-converting enzyme; NSAIDs: nonsteroidal anti-inflammatory drugs; COPD: Chronic obstructive pulmonary disease; AIDS: Acquired Immune Deficiency Syndrome.

6.2 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 PAM 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 4. In order to visualize the data set, a heatmap was obtained, taking into account variables with a p-value <0.05 (Figure 4). This graph represents the scaled values where intensities were color-coded to highlight possible patterns between groups.

Table 4. Characteristics of the different clusters.

	Cluster 1	Cluster 2	Cluster 3	p value
Participants	553 (45.4)	359 (29.5)	305 (25)	
Anthropometric and polygraphic variables				
Age (years)	51.1 (12.4) [50; 52.1]	63.4 (11) [62.2; 64.5]	64.5 (9.3) [63.5; 65.6]	<0.001
Sex				
Women	63 (11.4%) [8.9; 14.3]	50 (13.9%) [10.5; 17.9]	235 (77%) [71.9; 81.6]	<0.001
Men	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]	<0.001
ESS		7.5 (4.3) [7.1; 7.8]	8 (4.6) [7.5; 8.5]	5.9 (3.9) [5.4; 6.3]	<0.001
AHI		27.8 (20) [26.1; 29.5]	45.8 (26.9) [43; 48.5]	25.2 (17) [23.3; 27.1]	<0.001
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]	<0.001
	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]	<0.001
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]	<0.001
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]	<0.001
T90%		9.7 (14.6) [8.5; 10.9]	28.4 (29.3) [25.4; 31.5]	10.5 (17.5) [8.5; 12.5]	<0.001
ODI 3%		28 (21.4) [26.2; 29.8]	48.9 (29.4) [45.9; 52]	25 (19.2) [22.9; 27.2]	<0.001
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]	<0.001
Comorbidities					
Hypertension		113 (20.4%) [17.1; 24]	262 (73%) [68.1; 77.5]	195 (63.9%) [58.3; 69.3]	<0.001
Dyslipidemia		153 (27.7%) [24; 31.6]	274 (76.3%) [71.6; 80.6]	192 (63%) [57.3; 68.4]	<0.001
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]	<0.001
Ischaemic heart disease		5 (0.9%) [0.3; 2.1]	66 (18.4%) [14.5; 22.8]	19 (6.2%) [3.8; 9.6]	<0.001
Atrial fibrillation		5 (0.9%) [0.3; 2.1]	35 (9.7%) [6.9; 13.3]	15 (4.9%) [2.8; 8]	<0.001
COPD		25 (4.5%) [2.9; 6.6]	33 (9.2%) [6.4; 12.7]	24 (7.9%) [5.1; 11.5]	0.015
Depressive disorder		28 (5.1%) [3.4; 7.2]	34 (9.5%) [6.6; 13]	48 (15.7%) [11.8; 20.3]	<0.001
Solid neoplasm		17 (3.1%) [1.8; 4.9]	23 (6.4%) [4.1; 9.5]	18 (5.9%) [3.5; 9.2]	0.039
Other		65 (11.8%) [9.2; 14.7]	124 (34.5%) [29.6; 39.7]	72 (23.6%) [19; 28.8]	<0.001
Tobacco use		122 (22.1%) [18.7; 25.8]	77 (21.4%) [17.3; 26.1]	40 (13.1%) [9.5; 17.4]	0.004
Medicine prescription					
Beta blockers		7 (1.3%) [0.5; 2.6]	166 (46.2%) [41; 51.5]	22 (7.2%) [4.6; 10.7]	<0.001
Calcium blockers		15 (2.7%) [1.5; 4.4]	121 (33.7%) [28.8; 38.9]	57 (18.7%) [14.5; 23.5]	<0.001
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]	<0.001

Diuretics	34 (6.1%) [4.3; 8.5]	153 (42.6%) [37.4; 47.9]	96 (31.5%) [26.3; 37]	<0.001
Antihypertensives	7 (1.3%) [0.5; 2.6]	39 (10.9%) [7.8; 14.6]	16 (5.2%) [3; 8.4]	<0.001
Lipid lowering agents	62 (11.2%) [8.7; 14.1]	229 (63.8%) [58.6; 68.8]	149 (48.9%) [43.1; 54.6]	<0.001
Oral hypoglycemic agents	8 (1.4%) [0.6; 2.8]	142 (39.6%) [34.5; 44.8]	28 (9.2%) [6.2; 13]	<0.001
Insulins	4 (0.7%) [0.2; 1.8]	55 (15.3%) [11.8; 19.5]	10 (3.3%) [1.6; 5.9]	<0.001
Antiarrhythmics	7 (1.3%) [0.5; 2.6]	24 (6.7%) [4.3; 9.8]	18 (5.9%) [3.5; 9.2]	<0.001
Antiplatelets	21 (3.8%) [2.4; 5.7]	162 (45.1%) [39.9; 50.4]	70 (23%) [18.4; 28.1]	<0.001
Anticoagulants	10 (1.8%) [0.9; 3.3]	56 (15.6%) [12; 19.8]	18 (5.9%) [3.5; 9.2]	<0.001
Vasodilators for cardiac diseases	0 (0%) [0; 0.7]	29 (8.1%) [5.5; 11.4]	19 (6.2%) [3.8; 9.6]	<0.001
Bronchodilators	54 (9.8%) [7.4; 12.5]	101 (28.1%) [23.5; 33.1]	67 (22%) [17.4; 27]	<0.001
NSAIDs	115 (20.8%) [17.5; 24.4]	127 (35.4%) [30.4; 40.6]	207 (67.9%) [62.3; 73.1]	<0.001
Weak Opioids	11 (2%) [1; 3.5]	36 (10%) [7.1; 13.6]	46 (15.1%) [11.3; 19.6]	<0.001
Anxiolytics	48 (8.7%) [6.5; 11.3]	62 (17.3%) [13.5; 21.6]	122 (40%) [34.5; 45.7]	<0.001
Antidepressants	77 (13.9%) [11.1; 17.1]	73 (20.3%) [16.3; 24.9]	168 (55.1%) [49.3; 60.8]	<0.001
Hypnotics and Sedatives	8 (1.4%) [0.6; 2.8]	12 (3.3%) [1.7; 5.8]	34 (11.1%) [7.8; 15.2]	<0.001

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. BMI: body mass index; ESS: Epworth sleepiness scale; AHI: apnea-hypopnea index; SaO_2: oxygen saturation; T90: time percentage with SaO_2 < 90%; ODI: oxygen desaturation index; COPD: chronic obstructive pulmonary disease; NSAIDs: nonsteroidal anti-inflammatory drugs.

- ***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 (20)), without sleepiness (ESS 7.5 (4.3)) and slight nighttime hypoxemia (T90% 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 (26.9)), without sleepiness (ESS 8 (4.6)) and greater nocturnal hypoxemia (T90% 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%). It also showed the highest intake of medication related to cardiovascular risk factors and disease, compared with the other clusters: beta blockers (46.2%), calcium blockers (33.7%), angiotensin-converting enzyme inhibitors (74.7%), diuretics (42.6%), antihypertensives (10.9%), lipid lowering agents (63.8%), oral hypoglycemic agents (39.6%), insulins (15.3%), antiplatelets (45.1%), and anticoagulants (15.6%).

- ***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 (17)), without sleepiness (ESS 5.9 (3.9)) and slight nighttime desaturation (T90% 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%).

In clusters 1 and 2 (22.1% and 21.4%), tobacco use was similar and higher than cluster 3 (13.1%). Chronic obstructive pulmonary disease and the use of bronchodilators were similar in clusters 2 (9.2% and 28.1%) and 3 (7.9% and 22%). Solid neoplasms were more frequent in clusters 2 (6.4%) and 3 (5.9%), and cluster 2 had the highest frequency of "other" diseases (34.5%).

Figure 4. Heatmap representing intensities of the statistically significant variables.

Columns represent patients and lines the variables. Intensities are color-coded to highlight possible patterns between groups. For continuous variables blue is used for lower values and red for higher ones. For categorical variables the corresponding colors are "yellow/grey" for "male/female" gender and for "yes/no" scoring of the other variables. BMI: body mass index; NSAIDs: nonsteroidal

anti-inflammatory drugs; T90%: time percentage with oxygen saturation < 90%; SaO_2: oxygen saturation; ODI: oxygen desaturation index; AHI: apnea-hypopnea index; ACE: angiotensin-converting enzyme; COPD: chronic obstructive pulmonary disease.

6.3 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 5). Only the incidence of hypertension (13.4%) and dyslipidemia (20.3%) were similar to the other groups.

Clusters 2 and 3 presented similar incidences of cardiovascular risk factors: hypertension (15.3% and 13.1%, respectively), type2 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 (15.9% vs. 9.5%), ischaemic 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 5).

Table 5. Incidence of comorbidities in each cluster during follow-up.

	Cluster 1	Cluster 2	Cluster 3	p value
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]	<0.001
Comorbidities				
Hypertension	74 (13.4%) [10.7; 16.5]	55 (15.3%) [11.8; 19.5]	40 (13.1%) [9.5; 17.4]	0.68
Dyslipidemia	112 (20.3%) [17; 23.8]	68 (18.9%) [15; 23.4]	66 (21.6%) [17.1; 26.7]	0.69
Type 2 diabetes mellitus	47 (8.5%) [6.3; 11.1]	52 (14.5%) [11; 18.6]	50 (16.4%) [12.4; 21]	<0.001
Heart failure	11 (2%) [1; 3.5]	89 (24.8%) [20.4; 29.6]	29 (9.5%) [6.5; 13.4]	<0.001
Atrial fibrillation	20 (3.6%) [2.2; 5.5]	57 (15.9%) [12.3; 20.1]	29 (9.5%) [6.5; 13.4]	<0.001

Ischaemic heart disease	11 (2%) [1; 3.5]	52 (14.5%) [11; 18.6]	15 (4.9%) [2.8; 8]	<0.001
Cerebrovascular disease	11 (2%) [1; 3.5]	27 (7.5%) [5; 10.8]	16 (5.2%) [3; 8.4]	<0.001
Chronic kidney disease	17 (3.1%) [1.8; 4.9]	78 (21.7%) [17.6; 26.4]	32 (10.5%) [7.3; 14.5]	<0.001
Chronic obstructive pulmonary disease	21 (3.8%) [2.4; 5.7]	35 (9.7%) [6.9; 13.3]	15 (4.9%) [2.8; 8]	<0.001
Solid neoplasms	24 (4.3%) [2.8; 6.4]	30 (8.4%) [5.7; 11.7]	16 (5.2%) [3; 8.4]	0.04
Depressive disorder	24 (4.3%) [2.8; 6.4]	17 (4.7%) [2.8; 7.5]	36 (11.8%) [8.4; 16]	<0.001
Other	63 (11.4%) [8.9; 14.3]	76 (21.2%) [17.1; 25.8]	67 (22%) [17.4; 27]	<0.001

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-values shown in **bold** are statistically significant after Benjamini-Hochberg correction.

At the end of follow-up, the baseline differences in chronic medicine prescription between the clusters persisted (Table 6). 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 non-steroidal 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 (5.3% and 8.9%) and 3 (7.2% and 6.6%) compared to cluster 1 (1.8% and 4.7%).

Table 6. Medicine prescription at the end of follow-up in each cluster.

Medication	Cluster 1	Cluster 2	Cluster 3	p value
Beta blockers	38 (6.9%) [4.9; 9.3]	168 (46.8%) [41.5; 52.1]	44 (14.4%) [10.7; 18.9]	<0.001
Calcium blockers	36 (6.5%) [4.6; 8.9]	132 (36.8%) [31.8; 42]	68 (22.3%) [17.7; 27.4]	<0.001
Angiotensin-converting enzyme inhibitors	151 (27.3%) [23.6; 31.2]	279 (77.7%) [73.1; 81.9]	186 (61%) [55.3; 66.5]	<0.001
Diuretics	62 (11.2%) [8.7; 14.1]	164 (45.7%) [40.4; 51]	108 (35.4%) [30; 41.1]	<0.001

Antihypertensives	9 (1.6%) [0.7; 3.1]	42 (11.7%) [8.6; 15.5]	19 (6.2%) [3.8; 9.6]	<0.001
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]	<0.001
Insulins	10 (1.8%) [0.9; 3.3]	73 (20.3%) [16.3; 24.9]	14 (4.6%) [2.5; 7.6]	<0.001
Antiarrhythmics	8 (1.4%) [0.6; 2.8]	28 (7.8%) [5.2; 11.1]	19 (6.2%) [3.8; 9.6]	<0.001
Antiplatelets	52 (9.4%) [7.1; 12.1]	172 (47.9%) [42.6; 53.2]	84 (27.5%) [22.6; 32.9]	<0.001
Anticoagulants	19 (3.4%) [2.1; 5.3]	69 (19.2%) [15.3; 23.7]	37 (12.1%) [8.7; 16.3]	<0.001
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]	<0.001
Bronchodilators	81 (14.6%) [11.8; 17.9]	119 (33.1%) [28.3; 38.3]	87 (28.5%) [23.5; 33.9]	<0.001
Anxiolytics	79 (14.3%) [11.5; 17.5]	69 (19.2%) [15.3; 23.7]	124 (40.7%) [35.1; 46.4]	<0.001
Antidepressants	114 (20.6%) [17.3; 24.2]	89 (24.8%) [20.4; 29.6]	182 (59.7%) [53.9; 65.2]	<0.001
Hypnotics and Sedatives	22 (4%) [2.5; 6]	19 (5.3%) [3.2; 8.1]	38 (12.5%) [9; 16.7]	<0.001
Non-steroidal anti-inflammatory drugs	173 (31.3%) [27.4; 35.3]	113 (31.5%) [26.7; 36.6]	174 (57%) [51.3; 62.7]	<0.001
Corticosteroids	26 (4.7%) [3.1; 6.8]	32 (8.9%) [6.2; 12.4]	20 (6.6%) [4.1; 9.9]	0.04
Weak Opioids	32 (5.8%) [4; 8.1]	59 (16.4%) [12.8; 20.7]	82 (26.9%) [22; 32.2]	<0.001
Strong Opioids	10 (1.8%) [0.9; 3.3]	19 (5.3%) [3.2; 8.1]	22 (7.2%) [4.6; 10.7]	<0.001

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

Hospitalizations, causes of hospital admission, mortality and cause of death are depicted in Tables 7 and 8. 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), $p<0.001$). There were significant differences in some of the causes of hospitalization: cluster 2 showed the highest rates of hospitalizations caused by heart failure (15%), ischaemic heart disease (5.3%), 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 five years was significantly higher in cluster 2 compared to both cluster 3 and cluster 1 (12.3%, 5.9%, and 2.2%, respectively; p<0.001). There were no statistically significant differences in the cause of death between the three groups (Table 8).

Table 7. Hospital admissions in each cluster during follow-up.

	Cluster 1	Cluster 2	Cluster 3	p value
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]	<0.001
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]	<0.001
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]	<0.001
Ischaemic heart disease	5 (0.9%) [0.3; 2.1]	19 (5.3%) [3.2; 8.1]	3 (1%) [0.2; 2.8]	<0.001
Respiratory	21 (3.8%) [2.4; 5.7]	45 (12.5%) [9.3; 16.4]	24 (7.9%) [5.1; 11.5]	<0.001
Vascular	3 (0.5%) [0.1; 1.6]	9 (2.5%) [1.2; 4.7]	7 (2.3%) [0.9; 4.7]	0.04
Kidney disease	3 (0.5%) [0.1; 1.6]	22 (6.1%) [3.9; 9.1]	7 (2.3%) [0.9; 4.7]	<0.001
Digestive	17 (3.1%) [1.8; 4.9]	31 (8.6%) [5.9; 12]	13 (4.3%) [2.3; 7.2]	<0.001
Infectious	23 (4.2%) [2.7; 6.2]	44 (12.3%) [9; 16.1]	29 (9.5%) [6.5; 13.4]	<0.001
Neoplastic	30 (5.4%) [3.7; 7.7]	37 (10.3%) [7.4; 13.9]	28 (9.2%) [6.2; 13]	0.03
Ophthalmological	33 (6%) [4.1; 8.3]	42 (11.7%) [8.6; 15.5]	33 (10.8%) [7.6; 14.9]	0.01
Traumatological	37 (6.7%) [4.8; 9.1]	38 (10.6%) [7.6; 14.2]	55 (18%) [13.9; 22.8]	<0.001

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]. 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.

Table 8. Mortality and cause of death in the cohort and in each cluster during follow-up.

	All	Cluster 1	Cluster 2	Cluster 3	p value
Total deaths	74 (6.1%)	12 (2.2%)	44 (12.3%)	18 (5.9%)	<0.001
Cause of death					
Unknown	22 (29.7%) [19.7; 41.5]	2 (16.7%) [2.1; 48.4]	18 (40.9%) [26.3; 56.8]	2 (11.1%) [1.4; 34.7]	0.114
Neoplastic	23 (31.1%) [20.8; 42.9]	5 (41.7%) [15.2; 72.3]	13 (29.5%) [16.8; 45.2]	5 (27.8%) [9.7; 53.5]	
Heart Failure	3 (4.1%) [0.8; 11.4]	0 (0%) [0; 26.5]	3 (6.8%) [1.4; 18.7]	0 (0%) [0; 18.5]	
Ischaemic heart disease	3 (4.1%) [0.8; 11.4]	0 (0%) [0; 26.5]	1 (2.3%) [0.1; 12]	2 (11.1%) [1.4; 34.7]	
Infectious	5 (6.8%) [2.2; 15.1]	1 (8.3%) [0.2; 38.5]	2 (4.5%) [0.6; 15.5]	2 (11.1%) [1.4; 34.7]	
Neurodegenerative	5 (6.8%) [2.2; 15.1]	2 (16.7%) [2.1; 48.4]	1 (2.3%) [0.1; 12]	2 (11.1%) [1.4; 34.7]	
Respiratory	3 (4.1%) [0.8; 11.4]	0 (0%) [0; 26.5]	2 (4.5%) [0.6; 15.5]	1 (5.6%) [0.1; 27.3]	
Cerebrovascular	2 (2.7%) [0.3; 9.4]	1 (8.3%) [0.2; 38.5]	0 (0%) [0; 8]	1 (5.6%) [0.1; 27.3]	
Kidney disease	2 (2.7%) [0.3; 9.4]	0 (0%) [0; 26.5]	1 (2.3%) [0.1; 12]	1 (5.6%) [0.1; 27.3]	
Traumatic	2 (2.7%) [0.3; 9.4]	0 (0%) [0; 26.5]	1 (2.3%) [0.1; 12]	1 (5.6%) [0.1; 27.3]	
Liver disease	1 (1.4%) [0; 7.3]	0 (0%) [0; 26.5]	1 (2.3%) [0.1; 12]	0 (0%) [0; 18.5]	
Gastrointestinal bleeding	1 (1.4%) [0; 7.3]	1 (8.3%) [0.2; 38.5]	0 (0%) [0; 8]	0 (0%) [0; 18.5]	
Post-surgical complication	1 (1.4%) [0; 7.3]	0 (0%) [0; 26.5]	0 (0%) [0; 8]	1 (5.6%) [0.1; 27.3]	
Other	1 (1.4%) [0; 7.3]	0 (0%) [0; 26.5]	1 (2.3%) [0.1; 12]	0 (0%) [0; 18.5]	

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

6.4 Effect of CPAP treatment in the different clusters

CPAP treatment was prescribed to 237 subjects 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 users and No CPAP participants in the incidence of comorbidities, prescription of chronic medication, hospital admissions, or mortality (see Tables 9 to 12). In cluster 2, all-cause mortality was significantly higher in No CPAP participants compared to CPAP users (20% vs. 4%; $p<0.001$) but there were no differences in the cause of death (Table 12). 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%, $p=0.002$, Table 11). No significant differences were observed in the incidence of comorbidities or the prescription of chronic medication (Tables 9 and 10).

Table 9. Incidence of comorbidities in each cluster during follow-up, CPAP vs. No CPAP subgroups.

	Cluster 1			Cluster 2			Cluster 3		
	CPAP	No CPAP	p value	CPAP	No CPAP	p value	CPAP	No CPAP	p value
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]	0.544	1.2 (1.3) [1; 1.4]	1.1 (1.2) [1; 1.3]	0.74	1.1 (1) [0.9; 1.4]	1.1 (1.1) [0.9; 1.2]	0.362
Comorbidities									
Ischaemic heart disease	5 (2.9%) [0.9; 6.6]	6 (1.6%) [0.6; 3.4]	0.332	22 (12.6%) [8.1; 18.5]	30 (16.2%) [11.2; 22.3]	0.417	2 (2.1%) [0.3; 7.3]	13 (6.2%) [3.4; 10.4]	0.158
Depressive disorder	7 (4%) [1.6; 8.2]	17 (4.5%) [2.6; 7.1]	0.997	9 (5.2%) [2.4; 9.6]	8 (4.3%) [1.9; 8.3]	0.897	13 (13.5%) [7.4; 22]	23 (11%) [7.1; 16.1]	0.655
Type 2 diabetes	18 (10.4%) [6.3; 15.9]	29 (7.6%) [5.2; 10.8]	0.358	33 (19%) [13.4; 25.6]	19 (10.3%) [6.3; 15.6]	0.029	21 (21.9%) [14.1; 31.5]	29 (13.9%) [9.5; 19.3]	0.113
Dyslipidemia	41 (23.7%) [17.6; 30.7]	71 (18.7%) [14.9; 23]	0.213	35 (20.1%) [14.4; 26.8]	33 (17.8%) [12.6; 24.1]	0.678	18 (18.8%) [11.5; 28]	48 (23%) [17.4; 29.3]	0.496
Chronic kidney disease	3 (1.7%) [0.4; 5]	14 (3.7%) [2; 6.1]	0.334	31 (17.8%) [12.4; 24.3]	47 (25.4%) [19.3; 32.3]	0.106	7 (7.3%) [3; 14.4]	25 (12%) [7.9; 17.1]	0.301
COPD	6 (3.5%) [1.3; 7.4]	15 (3.9%) [2.2; 6.4]	0.973	20 (11.5%) [7.2; 17.2]	15 (8.1%) [4.6; 13]	0.367	4 (4.2%) [1.1; 10.3]	11 (5.3%) [2.7; 9.2]	0.783
Hypertension	23 (13.3%) [8.6; 19.3]	51 (13.4%) [10.2; 17.3]	1	29 (16.7%) [11.5; 23.1]	26 (14.1%) [9.4; 19.9]	0.589	14 (14.6%) [8.2; 23.3]	26 (12.4%) [8.3; 17.7]	0.74
Solid neoplasms	8 (4.6%) [2; 8.9]	16 (4.2%) [2.4; 6.7]	1	14 (8%) [4.5; 13.1]	16 (8.6%) [5; 13.7]	0.988	5 (5.2%) [1.7; 11.7]	11 (5.3%) [2.7; 9.2]	1
Other	21 (12.1%) [7.7; 18]	42 (11.1%) [8.1; 14.6]	0.819	36 (20.7%) [14.9; 27.5]	40 (21.6%) [15.9; 28.3]	0.931	20 (20.8%) [13.2; 30.3]	47 (22.5%) [17; 28.8]	0.861
Heart failure	2 (1.2%) [0.1; 4.1]	9 (2.4%) [1.1; 4.4]	0.516	34 (19.5%) [13.9; 26.2]	55 (29.7%) [23.2; 36.9]	0.035	6 (6.2%) [2.3; 13.1]	23 (11%) [7.1; 16.1]	0.269
Cerebrovascular disease	3 (1.7%) [0.4; 5]	8 (2.1%) [0.9; 4.1]	1	8 (4.6%) [2; 8.9]	19 (10.3%) [6.3; 15.6]	0.066	4 (4.2%) [1.1; 10.3]	12 (5.7%) [3; 9.8]	0.767
Atrial fibrillation	1 (0.6%) [0; 3.2]	19 (5%) [3; 7.7]	0.019	23 (13.2%) [8.6; 19.2]	34 (18.4%) [13.1; 24.7]	0.233	13 (13.5%) [7.4; 22]	16 (7.7%) [4.4; 12.1]	0.156

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]. All p-values are non-statistically significant after Benjamini-Hochberg correction. CPAP: continuous positive airway pressure.

Table 10. Medicine prescription at the end of follow-up in each cluster, CPAP vs. No CPAP subgroups.

	Cluster 1			Cluster 2			Cluster 3		
Medications	CPAP	No CPAP	p value	CPAP	No CPAP	p value	CPAP	No CPAP	p value
Beta blockers	16 (9.2%) [5.4; 14.6]	22 (5.8%) [3.7; 8.6]	0.19	83 (47.7%) [40.1; 55.4]	85 (45.9%) [38.6; 53.4]	0.82	15 (15.6%) [9; 24.5]	29 (13.9%) [9.5; 19.3]	0.81
Calcium blockers	9 (5.2%) [2.4; 9.6]	27 (7.1%) [4.7; 10.2]	0.51	69 (39.7%) [32.3; 47.3]	63 (34.1%) [27.3; 41.4]	0.32	26 (27.1%) [18.5; 37.1]	42 (20.1%) [14.9; 26.2]	0.22
Angiotensin-converting enzyme inhibitors	59 (34.1%) [27.1; 41.7]	92 (24.2%) [20; 28.8]	0.02	141 (81%) [74.4; 86.6]	138 (74.6%) [67.7; 80.7]	0.18	67 (69.8%) [59.6; 78.7]	119 (56.9%) [49.9; 63.7]	0.04
Diuretics	24 (13.9%) [9.1; 19.9]	38 (10%) [7.2; 13.5]	0.23	73 (42%) [34.5; 49.7]	91 (49.2%) [41.8; 56.6]	0.20	38 (39.6%) [29.7; 50.1]	70 (33.5%) [27.1; 40.3]	0.36
Antihypertensives	4 (2.3%) [0.6; 5.8]	5 (1.3%) [0.4; 3]	0.47	25 (14.4%) [9.5; 20.5]	17 (9.2%) [5.4; 14.3]	0.17	4 (4.2%) [1.1; 10.3]	15 (7.2%) [4.1; 11.6]	0.45
Lipid lowering agents	44 (25.4%) [19.1; 32.6]	78 (20.5%) [16.6; 24.9]	0.24	118 (67.8%) [60.3; 74.7]	130 (70.3%) [63.1; 76.8]	0.69	65 (67.7%) [57.4; 76.9]	122 (58.4%) [51.4; 65.1]	0.15
Oral hypoglycemic agents	17 (9.8%) [5.8; 15.3]	25 (6.6%) [4.3; 9.6]	0.24	75 (43.1%) [35.6; 50.8]	90 (48.6%) [41.2; 56.1]	0.34	20 (20.8%) [13.2; 30.3]	39 (18.7%) [13.6; 24.6]	0.77
Insulins	4 (2.3%) [0.6; 5.8]	6 (1.6%) [0.6; 3.4]	0.51	32 (18.4%) [12.9; 25]	41 (22.2%) [16.4; 28.8]	0.45	1 (1%) [0; 5.7]	13 (6.2%) [3.4; 10.4]	0.07
Antiarrhythmics	1 (0.6%) [0; 3.2]	7 (1.8%) [0.7; 3.8]	0.44	13 (7.5%) [4; 12.4]	15 (8.1%) [4.6; 13]	0.98	7 (7.3%) [3; 14.4]	12 (5.7%) [3; 9.8]	0.79
Antiplatelets	20 (11.6%) [7.2; 17.3]	32 (8.4%) [5.8; 11.7]	0.31	79 (45.4%) [37.9; 53.1]	93 (50.3%) [42.8; 57.7]	0.41	30 (31.2%) [22.2; 41.5]	54 (25.8%) [20; 32.3]	0.39
Anticoagulants	3 (1.7%) [0.4; 5]	16 (4.2%) [2.4; 6.7]	0.22	26 (14.9%) [10; 21.1]	43 (23.2%) [17.4; 30]	0.06	12 (12.5%) [6.6; 20.8]	25 (12%) [7.9; 17.1]	1

Vasodilators for cardiac diseases	2 (1.2%) [0.1; 4.1]	3 (0.8%) [0.2; 2.3]	0.65	23 (13.2%) [8.6; 19.2]	32 (17.3%) [12.1; 23.5]	0.35	6 (6.2%) [2.3; 13.1]	15 (7.2%) [4.1; 11.6]	0.95
Bronchodilators	24 (13.9%) [9.1; 19.9]	57 (15%) [11.6; 19]	0.83	62 (35.6%) [28.5; 43.2]	57 (30.8%) [24.2; 38]	0.39	28 (29.2%) [20.3; 39.3]	59 (28.2%) [22.2; 34.9]	0.97
Anxiolytics	22 (12.7%) [8.1; 18.6]	57 (15%) [11.6; 19]	0.56	31 (17.8%) [12.4; 24.3]	38 (20.5%) [15; 27.1]	0.60	41 (42.7%) [32.7; 53.2]	83 (39.7%) [33; 46.7]	0.71
Antidepressants	38 (22%) [16; 28.9]	76 (20%) [16.1; 24.4]	0.68	44 (25.3%) [19; 32.4]	45 (24.3%) [18.3; 31.2]	0.92	67 (69.8%) [59.6; 78.7]	115 (55%) [48; 61.9]	0.02
Hypnotics and Sedatives	5 (2.9%) [0.9; 6.6]	17 (4.5%) [2.6; 7.1]	0.52	11 (6.3%) [3.2; 11]	8 (4.3%) [1.9; 8.3]	0.54	10 (10.4%) [5.1; 18.3]	28 (13.4%) [9.1; 18.8]	0.58
Non-steroidal anti-inflammatory drugs	50 (28.9%) [22.3; 36.3]	123 (32.4%) [27.7; 37.3]	0.47	65 (37.4%) [30.2; 45]	48 (25.9%) [19.8; 32.9]	0.027	64 (66.7%) [56.3; 76]	110 (52.6%) [45.6; 59.6]	0.03
Corticosteroids	5 (2.9%) [0.9; 6.6]	21 (5.5%) [3.5; 8.3]	0.25	13 (7.5%) [4; 12.4]	19 (10.3%) [6.3; 15.6]	0.45	8 (8.3%) [3.7; 15.8]	12 (5.7%) [3; 9.8]	0.54
Weak Opioids	13 (7.5%) [4.1; 12.5]	19 (5%) [3; 7.7]	0.33	38 (21.8%) [15.9; 28.7]	21 (11.4%) [7.2; 16.8]	0.01	32 (33.3%) [24; 43.7]	50 (23.9%) [18.3; 30.3]	0.11
Strong Opioids	1 (0.6%) [0; 3.2]	9 (2.4%) [1.1; 4.4]	0.18	4 (2.3%) [0.6; 5.8]	15 (8.1%) [4.6; 13]	0.02	12 (12.5%) [6.6; 20.8]	10 (4.8%) [2.3; 8.6]	0.02

Data are shown as frequency (percentage) and [95% confidence interval]. All p-values are non-statistically significant after Benjamini-Hochberg correction. CPAP: continuous positive airway pressure.

Table 11. Hospitalizations in each cluster, CPAP vs. No CPAP subgroups.

	Cluster 1			Cluster 2			Cluster 3		
	CPAP	No CPAP	p value	CPAP	No CPAP	p value	CPAP	No CPAP	p value
Number of hospitalizations per participant	0.6 (1.1) [0.5; 0.8]	0.8 (1.4) [0.6; 0.9]	0.402	1.4 (2.2) [1.1; 1.7]	2.3 (3.1) [1.8; 2.7]	0.013	1 (1.2) [0.8; 1.2]	1.7 (2.6) [1.4; 2.1]	0.038
Number of participants that required hospitalization	63 (36.4%) [29.2; 44.1]	151 (39.7%) [34.8; 44.9]	0.516	99 (56.9%) [49.2; 64.4]	117 (63.2%) [55.9; 70.2]	0.263	52 (54.2%) [43.7; 64.4]	133 (63.6%) [56.7; 70.2]	0.148
Cause of hospitalization									
Autoimmune	0	0	-	0 (0%) [0; 2.1]	1 (0.5%) [0; 3]		0	0	-
Heart failure	1 (0.6%) [0; 3.2]	5 (1.3%) [0.4; 3]	0.671	15 (8.6%) [4.9; 13.8]	39 (21.1%) [15.4; 27.7]	0.002	1 (1%) [0; 5.7]	17 (8.1%) [4.8; 12.7]	0.029
Cerebrovascular	1 (0.6%) [0; 3.2]	7 (1.8%) [0.7; 3.8]	0.445	5 (2.9%) [0.9; 6.6]	8 (4.3%) [1.9; 8.3]	0.651	1 (1%) [0; 5.7]	5 (2.4%) [0.8; 5.5]	0.669
Ischaemic heart disease	2 (1.2%) [0.1; 4.1]	3 (0.8%) [0.2; 2.3]	0.65	9 (5.2%) [2.4; 9.6]	10 (5.4%) [2.6; 9.7]	1	0 (0%) [0; 3.8]	3 (1.4%) [0.3; 4.1]	0.554
Unknown	9 (5.2%) [2.4; 9.6]	10 (2.6%) [1.3; 4.8]	0.198	9 (5.2%) [2.4; 9.6]	8 (4.3%) [1.9; 8.3]	0.897	3 (3.1%) [0.6; 8.9]	12 (5.7%) [3; 9.8]	0.404
Digestive	5 (2.9%) [0.9; 6.6]	12 (3.2%) [1.6; 5.5]	1	12 (6.9%) [3.6; 11.7]	19 (10.3%) [6.3; 15.6]	0.342	3 (3.1%) [0.6; 8.9]	10 (4.8%) [2.3; 8.6]	0.761
Gynecologic	0 (0%) [0; 2.1]	4 (1.1%) [0.3; 2.7]	0.315	0	0	-	3 (3.1%) [0.6; 8.9]	10 (4.8%) [2.3; 8.6]	0.761
Hematologic	0 (0%) [0; 2.1]	1 (0.3%) [0; 1.5]	1	1 (0.6%) [0; 3.2]	2 (1.1%) [0.1; 3.9]	1	1 (1%) [0; 5.7]	0 (0%) [0; 1.7]	0.315
Infectious	7 (4%) [1.6; 8.2]	16 (4.2%) [2.4; 6.7]	1	18 (10.3%) [6.2; 15.9]	26 (14.1%) [9.4; 19.9]	0.363	9 (9.4%) [4.4; 17.1]	20 (9.6%) [5.9; 14.4]	1
Metabolic	1 (0.6%) [0; 3.2]	5 (1.3%) [0.4; 3]	0.671	3 (1.7%) [0.4; 5]	6 (3.2%) [1.2; 6.9]	0.504	6 (6.2%) [2.3; 13.1]	5 (2.4%) [0.8; 5.5]	0.106
Neoplastic	9 (5.2%) [2.4; 9.6]	21 (5.5%) [3.5; 8.3]	1	12 (6.9%) [3.6; 11.7]	25 (13.5%) [8.9; 19.3]	0.059	5 (5.2%) [1.7; 11.7]	23 (11%) [7.1; 16.1]	0.157

Neurodegenerative	0	0	-	1 (0.6%) [0; 3.2]	0 (0%) [0; 2]	0.485	0 (0%) [0; 3.8]	1 (0.5%) [0; 2.6]	1
Neurologic	1 (0.6%) [0; 3.2]	7 (1.8%) [0.7; 3.8]	0.445	1 (0.6%) [0; 3.2]	6 (3.2%) [1.2; 6.9]	0.123	4 (4.2%) [1.1; 10.3]	5 (2.4%) [0.8; 5.5]	0.47
Ophthalmologic	7 (4%) [1.6; 8.2]	26 (6.8%) [4.5; 9.9]	0.274	25 (14.4%) [9.5; 20.5]	17 (9.2%) [5.4; 14.3]	0.173	10 (10.4%) [5.1; 18.3]	23 (11%) [7.1; 16.1]	1
Psychiatric	0	0	-	0	0	-	1 (1%) [0; 5.7]	1 (0.5%) [0; 2.6]	0.531
Surgical	23 (13.3%) [8.6; 19.3]	33 (8.7%) [6.1; 12]	0.13	12 (6.9%) [3.6; 11.7]	13 (7%) [3.8; 11.7]	1	6 (6.2%) [2.3; 13.1]	20 (9.6%) [5.9; 14.4]	0.457
Renal	0 (0%) [0; 2.1]	3 (0.8%) [0.2; 2.3]	0.88	7 (4%) [1.6; 8.1]	15 (8.1%) [4.6; 13]	0.164	2 (2.1%) [0.3; 7.3]	5 (2.4%) [0.8; 5.5]	1
Respiratory	3 (1.7%) [0.4; 5]	18 (4.7%) [2.8; 7.4]	0.141	17 (9.8%) [5.8; 15.2]	28 (15.1%) [10.3; 21.1]	0.169	5 (5.2%) [1.7; 11.7]	19 (9.1%) [5.6; 13.8]	0.347
Toxic	0 (0%) [0; 2.1]	3 (0.8%) [0.2; 2.3]	0.556	0	0	-	0 (0%) [0; 3.8]	2 (1%) [0.1; 3.4]	1
Traumatologic	12 (6.9%) [3.6; 11.8]	25 (6.6%) [4.3; 9.6]	1	20 (11.5%) [7.2; 17.2]	18 (9.7%) [5.9; 14.9]	0.71	14 (14.6%) [8.2; 23.3]	41 (19.6%) [14.5; 25.7]	0.367
Urologic	9 (5.2%) [2.4; 9.6]	10 (2.6%) [1.3; 4.8]	0.198	8 (4.6%) [2; 8.9]	8 (4.3%) [1.9; 8.3]	1	1 (1%) [0; 5.7]	6 (2.9%) [1.1; 6.1]	0.439
Vascular	0 (0%) [0; 2.1]	3 (0.8%) [0.2; 2.3]	0.556	3 (1.7%) [0.4; 5]	6 (3.2%) [1.2; 6.9]	0.504	3 (3.1%) [0.6; 8.9]	4 (1.9%) [0.5; 4.8]	0.682
Pulmonary embolism	0	0	-	0 (0%) [0; 2.1]	2 (1.1%) [0.1; 3.9]	0.499	0	0	-

Data are shown as frequency (percentage) and [95% confidence interval], except for "Number of participants that required hospitalization" which is mean (standard deviation) and [95% confidence interval]. Only p-values shown in **bold** are statistically significant after Benjamini-Hochberg correction. CPAP: continuous positive airway pressure.

Table 12. Mortality and cause of death in each cluster, CPAP vs. No CPAP subgroups.

	Cluster 1			Cluster 2			Cluster 3		
	CPAP	No CPAP	p value	CPAP	No CPAP	p value	CPAP	No CPAP	p value
Mortality	0 (0%) [0; 2.1]	12 (3.2%) [1.6; 5.5]	0.022	7 (4%) [1.6; 8.1]	37 (20%) [14.5; 26.5]	<0.001	2 (2.1%) [0.3; 7.3]	16 (7.7%) [4.4; 12.1]	0.098
Cause of death									
Unknown	0	2 (16.7%) [2.1; 48.4]	1	4 (57.1%) [18.4; 90.1]	14 (37.8%) [22.5; 55.2]	0.79	1 (50%) [1.3; 98.7]	1 (6.2%) [0.2; 30.2]	1
Neoplastic	0	5 (41.7%) [15.2; 72.3]		2 (28.6%) [3.7; 71]	11 (29.7%) [15.9; 47]		1 (50%) [1.3; 98.7]	4 (25%) [7.3; 52.4]	
Heart Failure	0	0		0	3 (6.8%) [1.4; 18.7]		0	0	
Ischaemic heart disease	0	0		0	1 (2.7%) [0.1; 14.2]		0	2 (12.5%) [1.6; 38.3]	
Infectious	0	1 (8.3%) [0.2; 38.5]		0	2 (5.4%) [0.7; 18.2]		0	2 (12.5%) [1.6; 38.3]	
Neurodegenerative	0	2 (16.7%) [2.1; 48.4]		0	1 (2.7%) [0.1; 14.2]		0	2 (12.5%) [1.6; 38.3]	
Respiratory	0	0		0	2 (5.4%) [0.7; 18.2]		0	1 (6.2%) [0.2; 30.2]	
Cerebrovascular	0	1 (8.3%) [0.2; 38.5]		0	0		0	1 (6.2%) [0.2; 30.2]	
Kidney disease	0	0		0	1 (2.7%) [0.1; 14.2]		0	1 (6.2%) [0.2; 30.2]	
Traumatic	0	0		1 (14.3%) [0.4; 57.9]	0		0	1 (6.2%) [0.2; 30.2]	
Liver disease	0	0		0	1 (2.7%) [0.1; 14.2]		0	0	
Gastrointestinal bleeding	0	1 (8.3%) [0.2; 38.5]		0	0		0	0	

Post-surgical complication	0	0	0	0	0	1 (6.2%) [0.2; 30.2]
Other	0	0	0	1 (2.7%) [0.1; 14.2]	0	0

Data are shown as frequency (percentage) and [95% confidence interval]. Only p-values shown in **bold** are statistically significant after Benjamini-Hochberg correction. CPAP: continuous positive airway pressure.

Table 13. Summary of the effect of CPAP treatment in each cluster.

	Cluster 1			Cluster 2			Cluster 3		
	CPAP	No CPAP	p value	CPAP	No CPAP	p value	CPAP	No CPAP	p value
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]	0.544	1.2 (1.3) [1; 1.4]	1.1 (1.2) [1; 1.3]	0.74	1.1 (1) [0.9; 1.4]	1.1 (1.1) [0.9; 1.2]	0.362
Deaths	0 (0%) [0; 2.1]	12 (3.2%) [1.6; 5.5]	0.022	**7 (4%) [1.6; 8.1]**	**37 (20%) [14.5; 26.5]**	**<0.001**	2 (2.1%) [0.3; 7.3]	16 (7.7%) [4.4; 12.1]	0.098
Number of hospitalizations per participant	0.6 (1.1) [0.5; 0.8]	0.8 (1.4) [0.6; 0.9]	0.402	1.4 (2.2) [1.1; 1.7]	2.3 (3.1) [1.8; 2.7]	0.013	1 (1.2) [0.8; 1.2]	1.7 (2.6) [1.4; 2.1]	0.038
Total number of participants that required hospitalization	63 (36.4%) [29.2; 44.1]	151 (39.7%) [34.8; 44.9]	0.516	99 (56.9%) [49.2; 64.4]	117 (63.2%) [55.9; 70.2]	0.263	52 (54.2%) [43.7; 64.4]	133 (63.6%) [56.7; 70.2]	0.148

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. Only p-values shown in **bold** are statistically significant after Benjamini-Hochberg correction. CPAP: continuous positive airway pressure.

Results from Cox proportional hazards are summarized in Table 14 and Figure 5.

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.

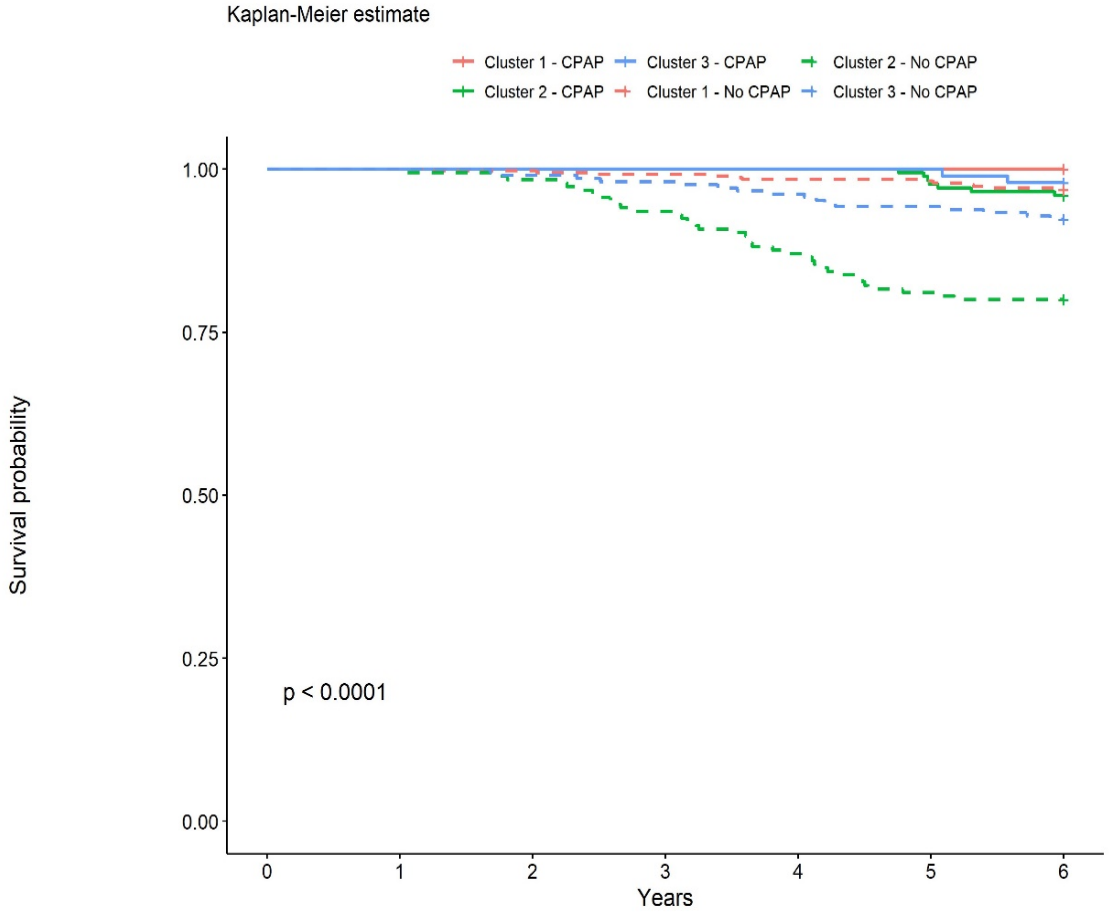
Individuals who did not receive CPAP treatment were at increased risk of death when compared with those who were treated with CPAP (HR 5.84, CI 2.9-11.8, p<0.001). The difference in mortality, according to CPAP treatment, was observed from the second year of follow-up. This risk was higher in clusters 2 and 3, compared with cluster 1 (HR 7.7, CI 4.06-14.63, p<0.001, and HR 2.79, CI 1.34-5.79, p=0.006, respectively).

Table 14. Cox Proportional Hazards Models assessing all-cause mortality.

	HR	(95% CI)	p value
CPAP users vs. No CPAP	5.84	2.9-11.8	<0.001
Cluster 2	7.7	4.06-14.63	<0.001
Cluster 3	2.79	1.34-5.79	0.006

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

Figure 5. Kaplan-Meier survival probability curves for all-cause mortality.



Dotted lines represent the No CPAP groups. CPAP: continuous positive airway pressure.

7. DISCUSSION

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 of all, 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 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[286,288,290,295], 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[297]. Secondly, 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[293,297,299,303]. 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 different nature like metabolic, respiratory, kidney, liver diseases, and psychological conditions[62]. Few studies have analyzed other aspects in the long term. Gagnadoux et al., in clusters identified using symptoms and comorbidities, examined CPAP treatment success at six 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[289]. Pien et al. studied treatment response patterns, BMI, quality of life, and comorbidities during two years, in clusters defined mainly by symptomatology[306]. 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. Different studies show that OSA is related mainly to obesity, hypertension, and diabetes mellitus, which prevalence increases with age and also with CVD and arrhythmias, especially in men from the sixth decade of life[62,312]. Assuming that cluster 2 represents the natural evolution of cluster 1, approximately 10-15 years later, this enhances the need to improve 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=0.04). As age was similar in clusters 2 and 3, other characteristics in patients of group 2 (e.g., 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 real higher prevalence of depression and anxiety, than that obtained by disease-coding and that described in the general population. An epidemiological study in the general population of Spain showed that the lifetime prevalence of a major depressive disorder was 14.5% for adult women and reached 17.9% at ages 50 to 64[313]. The disparity between the percentages of diagnosis and medication prescription should be interpreted with caution since some anxiolytics and antidepressants (e.g., lorazepam, mirtazapine, and trazodone) could have been prescribed to treat insomnia. On the other hand, insomnia had a very low prevalence in our cohort (falling in the "Other" diagnostic category), despite the female cluster showing a

significant intake of hypnotics and sedatives (11.1%). This could be explained by the fact that, frequently, insomnia is not a recognized pathology, and it might be considered just a symptom of other diseases, like depression. Other cluster analyses have found similar predominantly female phenotypes with symptoms of insomnia or "disturbed sleep"[294,295,299], depression, obesity, and associated comorbidities (hypertension and type 2 diabetes)[289,304]. Our findings are consistent with multiple studies that suggest that OSA behaves differently in men than in women. It has been reported that OSA patients, and particularly females, have a higher prevalence and a higher risk of developing depression at 1-year follow up, than the general population[62,225,314]. Women also have more "atypical" symptoms of OSA: insomnia, fatigue, morning headaches, impaired memory, mood disturbances[315]; they are less likely to have an ESS >10[316] and have a worse quality of life, especially when coexisting with insomnia[317].

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. Epidemiological and experimental studies suggest that the relationship between pain and sleep disturbances is bidirectional: people with chronic pain often suffer from sleep disturbances, and sleep disturbances might exacerbate pain[318,319]. Chronic pain is also linked to depression[320]. Additionally, painkillers like opioids can cause daytime sleepiness[321], alter sleep architecture[322], induce central sleep apneas, and ataxic breathing[323]. Although it has been hypothesized that sleep fragmentation in OSA patients could be associated with hyperalgesia, the direct relationship between pain and OSA, or its response to CPAP treatment, has not been deeply studied, with only a few studies with a small number of subjects showing mixed results[324–327].

This phenotype also had the highest rate of hospitalizations for traumatological reasons.

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 higher in clusters 2 and 3 compared to 1. This supports the importance of treating moderate-severe OSA with CPAP, but it also raises the need for early consideration of alternative options to CPAP in young, moderate OSA 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[328].

The older clusters with comorbidities showed a greater benefit 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)[13]. 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[117–119], even though methodological biases have been suggested as likely explanations[122]. Clusters 1 and 3 had moderate OSA. Some studies have found a protective role of CPAP on cardiovascular events only in severe OSA[88], but others have found it also in mild and moderate disease[114,329]. 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[116]. 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[88], 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[330]. Another recent long-term prospective clinical cohort study found that CPAP therapy was associated with reduced all-cause mortality in both men and women[329]. 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[13]. Few studies focusing on women have analyzed other CPAP outcomes, like those related to the quality of life, with inconsistent results[226,289]. 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[331]. 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[310]. CPAP compliance was similar in the 3 groups in those patients who continued treatment at follow-up.

7.1 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 to have considered gender-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 AQuAS, ensure that it is trustworthy. Although we do not have detailed information on symptoms, unlike some previous cluster analyses[286,294,299], we have used the ESS, the most common tool in all studies and clinical practice to assess the degree of subjective sleepiness, which together with the data on comorbidities and chronic medications, provide 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[332]. 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.

8. CONCLUSIONS

CONCLUSIONS

1. We identified three different clusters with different outcomes in a 5-year follow-up. Two predominantly men clusters: one middle-aged with moderate OSA, another one older, with severe OSA and comorbidities; and a female predominant cluster with moderate OSA, depression, anxiety, insomnia, and chronic pain.

2. During follow-up, the clusters maintained differentiated characteristics regarding comorbidities, medication intake, hospitalizations, and mortality, allowing the validation of the phenotypes. In the longer-term, the younger men cluster could evolve to become the older men cluster with comorbidities.

3. In the female predominant OSA cluster, the relevant prevalence of mood disorders, chronic pain, and their pharmacological treatment, generates a need for future research to improve clinical recognition and management of OSA in women.

4. The risk of mortality was significantly higher in patients not treated with CPAP (CPAP not prescribed or discontinued) compared to those treated. This risk was higher in the older clusters (clusters 2 and 3) compared to the youngest (cluster 1). This supports the importance of treating moderate-severe OSA with CPAP, and of considering alternative options to CPAP in young, moderate OSA without comorbidities and in those not willing to use this treatment.

9. FUTURE RESEARCH

FUTURE RESEARCH

Identifying clinical phenotypes through cluster analysis is just the first step towards developing personalized medicine strategies in OSA.

Identified clusters should be confirmed in different prospective cohorts and validated regarding clinical outcomes. Following studies should focus on investigating the pathophysiology that explains the different phenotypes and getting a more comprehensive understanding of the differences in individual susceptibility to the systemic effects and end-organ damages inflicted by OSA. In addition, cluster derived phenotypes may constitute a way to refine the assessment of the usefulness of CPAP on OSA patients in clinical trials.

Particularly from our study, many questions arise regarding issues that should be examined in greater depth:

- The susceptibility of younger patients with mild to moderate disease to develop end-organ damage, especially cardiovascular disease. The impact of CPAP and other treatment options for this phenotype (such as oral appliances, lifestyle interventions, and drug therapy to lose weight).
- The bidirectional relationship between OSA, psychiatric diseases and their pharmacological treatment, especially in the female population. Understanding the pathophysiological mechanism behind them. Developing screening tools to identify psychiatric disorders or mood disturbances among OSA patients (and vice versa). The evaluation of benefits of treating OSA in this phenotype not just related to mortality (symptoms, quality of life).
- The relationship between OSA, chronic pain, and its pharmacological treatment in particular OSA groups. Evaluation in different cohorts. Evaluation of treatment options.

Determining the severity of OSA should not continue to rely solely on the AHI. Classification of patients with OSA should incorporate other features like symptoms, comorbidities, and pathophysiological traits. In this way, individual treatment options could be offered according to each phenotype's characteristics, leading to a more significant therapeutic success and efficient use of healthcare resources.

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11. ANNEXES

11.1 PUBLICATION 1

Silveira MG, Sampol G, Mota-Foix M, Ferrer J, Lloberes P. Cluster-derived obstructive sleep apnea phenotypes and outcomes at 5-year follow-up. J Clin Sleep Med. 2022 Feb 1;18(2):597-607.

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11.2 PUBLICATION 2

Silveira MG, Lloberes P. Cluster Analysis to Identify Apnea-Hypopnea Syndrome Phenotypes: Where Are We Heading? Arch Bronconeumol (Engl Ed). 2020 Nov;56(11):689-690. English, Spanish.

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