Universitat de Girona
Facultat de Medicina

The prevalence of Sleep Apnea and Hypopnea Syndrome among patients with recent diagnosis of hypertension

A cross-sectional study

Author: **Berta Roca Portella**
Tutors: **Dr. Ramon Orriols, Dra. Susana Mota**

November 2015- January 2016

Hospital Universitari de Girona Doctor Josep Trueta

Universitat de Girona

I would like to express my sincere gratitude to all the staff of the Respiratory Service of Hospital Universitari Josep Trueta of Girona for having received me so well.

I want to thank very much Dr. Ramon Orriols who has been the tutor of this project.

Especial thanks to Dra. Susana Mota and to Dr. Anton Obrador, both with great experience in this area, who helped me with everything they could.

I would also like to thank Dr. Abel López for guiding me through the methodological aspects of the project.

Girona, January 2016

Index

1. ABBREVIATIONS

ABS	Àrea Bàsica de Salut
AHI	Apnea Hypopnea Index
BMI	Body Mass Index
BP	Blood Pressure
CAP	Centre d'Atenció Primària
CPAP	Continuous Positive Airway Pressure
DBP	Diastolic Blood Pressure
ECAP	Estación Clínica de Atención Primaria
EEG	Electroencephalogram
OSA	Obstructive Sleep Apnea
OSAS	Obstructive Sleep Apnea Syndrome
PG	Poligraphy
PSG	Polisomnography
RDI	Respiratory Disturbance Index
RERA	Respiratory Effort Related Arousal
SAHS	Sleep Apnea and Hypopnea Syndrome
SBP	Systolic Blood Pressure
SEPAR	Sociedad Española de Neumología y Cirugía Torácica

2. ABSTRACT

Introduction: Sleep apnea and hypopnea syndrome (SAHS) is a very prevalent disorder that has severe consequences if it is not correctly treated. However, there is still an important SAHS underdiagnose. One of the most studied associations among SAHS patients is hypertension, which is also related to the severity of the disease.

Justification: At present, there is no evidence about the real prevalence of SAHS in patients diagnosed of recent hypertension. All data come from studies that determine SAHS prevalence in long-term hypertension. If a high sleep respiratory disorders prevalence among those patients is found, we would be able to propose therapeutic strategies for SAHS when a patient would be diagnosed of hypertension. As a result, we would be able to avoid morbidity and mortality of untreated SAHS.

Objectives: The main objective of this study is to quantify the prevalence of patients with SAHS who have been diagnosed as having recent hypertension (less than one year) in primary care. The secondary objective is to analyze the prevalence of SAHS among the different stages of recent hypertension.

Methodology: A 16-month, observational, cross-sectional study including 246 patients will be carried out in the primary care centers of Girona and in its tertiary university referral hospital (Hospital Universitari Doctor Josep Trueta). The participants will be the patients selected from a computerized medical record (ECAP) diagnosed of hypertension during the last year in one of these primary care centers. We will stratify the sample by age and gender. The main variable will be the presence of SAHS. We will perform a polygraphy (ApneaLink©) to all the participants, and so we will measure the prevalence of SAHS among them and the prevalence of SAHS by hypertension severity groups, with a descriptive analysis and a bivariate analysis, respectively. In order to avoid potential confounders, we will perform a multivariate analysis adjusted for the covariates.

Key words: Sleep apnea and hypopnea syndrome, hypertension, primary care, polygraphy.

3. INTRODUCTION

1. What is sleep apnea and hypopnea syndrome (SAHS)?

Before the international classification of sleep disorders of the American Academy of Sleep medicine was made in 1990 (1), it was very difficult to define SAHS because there was lack of standard definitions of abnormal breathing events during sleep. Since then there have been a lot of modifications but it is still confusing.

1. Concept

To understand the concept of SAHS it is necessary to define previously the apnea, hypopnea, respiratory effort-related arousal (RERA) and the apnea and hypopnea index (AHI) concepts:

We understand **apnea** as the absence of airflow or its reduction greater than ≥90% of the baseline that lasts ≥10 seconds recorded by oronasal thermistors and/ or nasal pressure cannulas. It can be central if there is an absence of respiratory effort throughout the event, or obstructive if there is effort to breathe. Also, it can be a mixed apnea if it begins as a central one, but before the end there is an effort to breathe without airflow (2,3).

Hypopnea is the concept that has had more different definitions. Nowadays is defined as a reduction in airflow between 30% - 90% that lasts ≥ 10 seconds, or an important decrease of the thoraco-abdominal movements (>30% compared to baseline), associated with desaturation (≥ 3% from baseline prior to the event) and/or an arousal in the electroencephalogram (EEG) (2,3).

The **respiratory effort-related arousal (RERA)** is defined as an increase of the respiratory effort that lasts more than 10 seconds and resolves with an arousal, without airflow reduction (2,3).

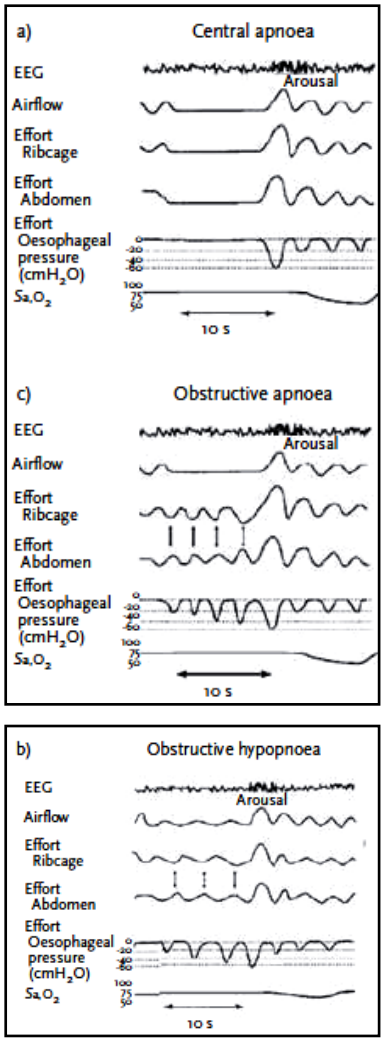


Figure 1: Presentations of apnea and hypopnea (12)

To define SAHS and its severity we have to take into account the **apnea-hypopnea index (AHI),** which is defined as the number of apneas and hypopneas per hour of sleep; or the **respiratory disturbance index (RDI)**, that is defined as the number of apneas, hypopneas and RERA per hour of sleep. However, in the practice we can use them as the same concept, assuming that RERA are included as hypopneas (3).

2. Definition of SAHS

The "Sociedad Española de Neumología y Cirugía Torácica" (SEPAR) (3) agreed in 2011 that, despite the "Documento nacional de consenso" in 2005 (4) defined SAHS as an "excessive daytime sleepiness, cognitive behavioral, respiratory, cardiac, metabolic or inflammatory disorder, due to a repeated episodes of superior airway obstruction during sleep (RDI >5 per hour) ", this definition has some limitations. SEPAR consider that an RDI >5 could not be pathologic; as an elevated RDI could not be associated with daytime sleepiness (5).

As a result, nowadays there are two different related definitions although in the practice they are often used indistinctly (6):

- **Obstructive sleep apnea (OSA)**: Defined by the number of obstructive apnea and hypopnea episodes per hour of sleep (AHI).
- **Sleep apnea and hypopnea syndrome (SAHS)** or **OSA syndrome (OSAS)**: defined by an elevated AHI in conjunction with hyper-somnolence or related problems in daytime functions.

However, there are standard diagnostic criteria for SAHS, but not all the patients accomplish these criteria. Due to the pluriphenotypical expression of SAHS, some people could respond to the standard criteria (An elevated AHI associated with daytime sleepiness), but others can present only SAHS complications without symptoms or, moreover, they could present only an elevated AHI (3,7). Therefore, we will be able to treat like SAHS those patients with an RDI > 15 without symptoms but cardiovascular antecedents; and those with an RDI > 30 even if the patient has no symptoms (3).

The **severity** of the syndrome is established by the AHI according to the following criteria (2,8):

1. Mild: ≥5 and <15 events per hour.
2. Moderate: ≥15 to ≤30 events per hour.
3. Severe: greater than 30 events per hour.

Diagnostic criteria for SAHS (3):

AHI > 5 per hour, associated with one of the following:

A. Excessive daytime sleepiness, not explained by other causes.

B. Two or more of the following criteria:

B.1. Nocturnal choking

B.2. Frequent awakenings

B.3. Non refreshing sleep

B.4. Fatigue during the day

B.5. Concentrating difficulties

3. Prevalence of SAHS

SAHS is a very prevalent entity because about 4% of men and 2% of women in their middle-ages have symptomatic SAHS and about 24% of men and 9% of women have an abnormal AHI (AHI >5/hour) (6,9). In 2013, the estimated prevalence of patients with an AHI >15 per hour was 10% in men among 30-49 years old and 17% in men among 50-70 years old. The prevalence in women is minor, with about 3% of 30-49 years old and 9% of 50-70 years old (10). Also, defining SAHS as an AHI >10 per hour plus excessive daytime sleepiness, the prevalence of SAHS found was about 3.4% in men and 3% in women (5). It is estimated that in Spain there are between 5 to 7 million people who suffers SAHS but only 5-9% are correctly diagnosed (7). In addition, the prevalence is increasing because of the recent obesity epidemic and population aging increase.

4. Clinical characteristics of SAHS

The main clinical signs of SAHS are chronic snoring, observed apneas and excessive daytime sleepiness (3), but there are other important symptoms showed in table 1.

None of the symptoms individually or in combination with others, can diagnose by itself SAHS. These symptoms appear frequently in healthy people and they may be absents in sleep apnea and hypopnea syndrome (5).

Loud snoring is the main symptom of SAHS and the most sensitive one. As a result, it is improbable to have SAHS without it. Observed apneas are the most specific symptom, and excessive daytime sleepiness is the most important one because it directly correlates with the severity of SAHS (3). We can quantify the excessive daytime sleepiness with Epworth Scale, which has a validated Spanish version (*Annex 1*) (11).

Table 1: SAHS symptoms (7,12)	
Diurnal symptoms	**Nocturnal symptoms**
Excessive daytime sleepiness	Loud Snoring
Non-refreshing sleep	Witnessed apneas
Chronic fatigue	Nocturnal choking
Morning headaches	Abnormal movements
Irritability, mood changes	Nocturnal sweating
Apathy	Frequent awakenings
Depression	Nocturnal diuresis, enuresis
Difficulty concentrating	Nightmares
Memory loss	Disturbed, unrefreshing sleep
Libido decrease	Insomnia
Character changes	Gastro-esophageal reflux
Morning dry mouth	Thirst during the night

5. Diagnosis of SAHS

The gold standard method to diagnose SAHS is the **polysomnography (PSG)** (4). It is a very sensitive and specific method because it captures a minimum of 7 channels of data (including respiratory, cardiovascular and neurologic parameters). The disadvantages of the PSG are that it requires spending the night in a sleep laboratory and the supervision of a sleep expert technician, so PSG is very expensive and there is frequently a long waiting time for its realization (13).

The respiratory **poligraphy (PG)** is another diagnostic method that uses portable monitors, which allow performing the sleep study in the patient's home. The advantage of this method is that is more accessible and less expensive than the PSG. The main disadvantage is that it is less complete than the PGS. It only records the respiratory effort, the pulse, the oxygen saturation and the nasal flow during sleep; it does not record the sleep variables, only the respiratory ones. Therefore, it can underdiagnose SAHS because it has less sensitivity than PSG, and underestimates its severity (3).

Nevertheless, PG is considered convenient for diagnosing SAHS in patients with moderate to high pretest probability of SAHS without substantial comorbidities (13). The usefulness of PG in low pretest probability cases is not fully validated, but is habitual in clinical practice (3).

6. The underdiagnose of SAHS

Since the high prevalence of SAHS in adults was uncovered, scientists thought about a probable underdiagnose of SAHS, and in 1997, Young and coworkers estimate that 93% of women and 82% of men with moderate to severe SAHS and about 98% of women and 90 % of men with mild SAHS were missed (14). It means that only 10% of SAHS population is diagnosed and treated.

In a population based study in 2001, they have found that 5.8% of men and 11.2% of women not suspected of having SAHS met criteria on polysomnography (5). Other studies show that there are a 5% of underdiagnosed SAHS, but they do not count the large proportion of people with asymptomatic SAHS (6). So, if we determine the prevalence of SAHS based on an abnormal RDI, the potential SAHS burden in the population is extremely important (6,7).

7. Risk factors for SAHS

There is a number of risk factors for developing SAHS, and people with these factors should be evaluated (Table 2) (6,12):

Table 2: Risk factors for SAHS (7)	
Obesity	Sedative drugs
Male gender	Adenoidectomy and/or tonsillectomy
Age	Postmenopausal status
Family history of SAHS	Hypothyroidism, acromegaly, polycystic ovary
Alcohol and smoking habit	Down syndrome

8. Consequences of SAHS

Untreated SAHS has dangerous health consequences and there is a relation between the severity of SAHS and cardiovascular risk (15).

- **Cardiovascular consequences**:

  The pathophysiological interaction between SAHS and cardiovascular diseases is complex, and comprises neural, humoral, mechanical, hemodynamic and circadian rhythm components (12).

  During the apnea, the hypoxemia and hypercapnia stimulate the chemoreceptors and breathing absence blocks the inhibitory sympathetic afferents, resulting in an increase of the sympathetic tone. This high sympathetic tone produce generalized vasoconstriction, and consequently, rise of blood pressure and more myocardia oxygen consumption (3).

The apneas also produce intrathoracic pressure changes due to an increased inspiratory effort, which produces raised cardiac right preload, and both ventricles afterload. The result is a reduction of the systolic final volume and the absence of diastolic relaxation.

Also, the repeated episodes of deoxygenation and re-oxygenation induce excessive production of free radicals of oxygen, proinflammatory cytokines, circulating inflammatory cells, C-reactive protein and endothelial adhesion molecules. These changes promote endothelial dysfunction and promote atherosclerosis formation with hypercoagulability (3,6).

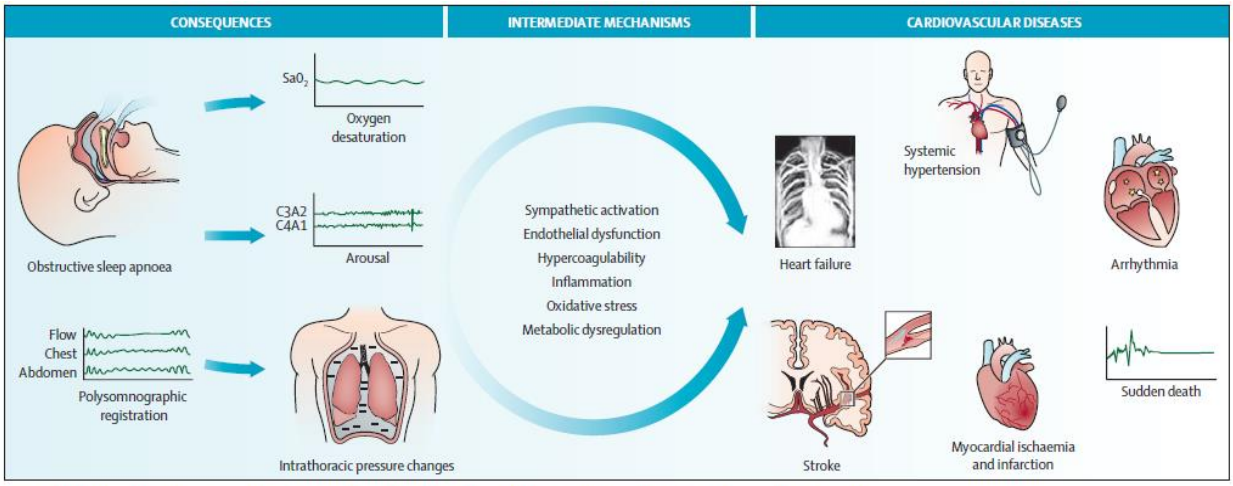


***Figure*: Obstructive sleep apnoea consequences and intermediate mechanisms that potentially contribute to risk of cardiovascular disease**
The events associated with collapse of the upper airway lead to brain arousal, intrathoracic pressure changes, and hypoxaemia and reoxygenation. Several intermediate mechanisms link obstructive sleep apnoea with the initiation and progression of cardiovascular diseases. SaO_2=oxygen saturation. C3A2 and C4A1=electroencephalographic channels.

Figure 2: Cardiovascular consequences (16)

Due to these mechanisms, SAHS is associated with cardiovascular diseases like (3,6,15–18):

- Hypertension (See section: "The association between SAHS and hypertension")
- Heart failure: The most directly related mechanism is hypertension, but other grow factors and the increased negative intrathoracic pressure can also contribute to heart failure.
- Arrhythmias: Arrhythmias occur in 50% of SAHS, especially atrial fibrillation.
- Ischemic heart disease: Due to atherosclerosis produced by vascular injury.
- Stroke: It is shown that 60-80% of people who have suffered a stroke or a transient ischemic attack have an AHI >10. And 25% of patients with severe SAHS have silent cerebral infarcts. It is because of the increased risk of plaque ruptures.
- Pulmonary arterial hypertension: It is estimated that the prevalence of pulmonary hypertension is 17% in SAHS with AHI >20 but it is predominantly slight. It produces heart hypertrophy and heart failure.
- Sudden death.
- Pulmonary embolism: It is more prevalent in SAHS patients and there are an independent association between SAHS and pulmonary embolism.

• **Mortality, death from other causes**:

It is shown that moderate-severe SAHS is associated with 33% mortality over 14 years compared to 6.5% and 7.7% mortality in people with mild or no SAHS, respectively (19). Moreover, the association between SAHS and mortality is still significant after adjustment for age, gender, blood pressure, cholesterol, Body Mass Index (BMI), DM, angina and smoking (19,20).

Therefore, SAHS is an independent risk factor for all-cause mortality and we have to take into account in the list of standard mortality risk factors, mostly for male gender (19,21).

• **Neurobehavioral consequences:**

One of the most important consequences of SAHS is daytime sleepiness, which impairs executive functions and effects the patients quality of life (12).

In addition, sleep process is important in memory reprocessing, consolidating and forming our declarative, procedural and cognitive memories (12). Therefore, because SAHS patients have sleep disturbance, they would suffer some effects on cerebral function, like slowing of information process independently of fatigue or daytime sleepiness. The effect of an increase in AHI of 15 is estimated to be approximately equivalent to the effect of 5 years of aging on psychomotor function (6). It is more important in children and adolescents, where the brain is still developing (12).

Furthermore, 40% of patients with SAHS suffer depression, but there is lack of evidence for a longitudinal association between SAHS and depression (21).

• **Endocrine effects:**

SAHS has an important impact on the adipocyte activity and the metabolic syndrome because of the intermittent hypoxia. It causes a pro-inflammatory state and neurohumoral activation due to the related stress of hypoxemia.

It is shown that sleep restriction causes insulin resistance, reduced leptin and increased ghrelin plasma concentration, and an increased appetite. In conclusion, patients with SAHS have five-fold risk of metabolic syndrome compared to healthy patients (12).

However, a systematic review shows that there is only a little published evidence of a longitudinal association between SAHS and diabetes (21).

- **Driving and traffic crashes:**

It is demonstrated that patients with SAHS have clearly an increased risk for traffic accidents (7,22). Since loss states affect the maintenance of lane positions, reaction time and steering, SAHS patients are more likely to suffer crashes; being AHI the best predictor factor for crashes (7).

The patients with SAHS have a mean crash ratio about 1.21 to 4.89. It means that, if a healthy driver has a risk about 0.08 crashes per person-year, the SAHS patient can be expected to be in the range of 0.10 to 0.39 crashes per person-year (22). And people with AHI>15 have an odds ratio of 7.3 for multiple crashes in a 5-years period (6) and it increases to 11 with alcohol consumption (7).

SAHS is also an independent risk factor for crashes regardless of sleepiness. In fact, if patients do not perceive sleepiness they may not be likely to take extra-precautions when driving, so they would have an even more increased crash risk (6).
So we can conclude that, SAHS is a serious public health problem, and it affects all people who drive.

- **Cancer:**

It is shown that intermittent hypoxia is associated with oxidative stress and inflammatory transcription factors increase, and these are potentials factors to develop cancer, accelerate tumor growth and increase resistance to treatments. Consequently, there is demonstrated that overnight hypoxia is independently associated with increased cancer mortality. And this is stronger when SAHS is more severe and in young people <65 years old (23).

9. Treatment of SAHS

- Sleep hygiene: It is important to reduce daytime sleepiness having regular sleep habits, and do not smoke or intake alcohol or caffeine before nighttime. Also it is recommended to sleep in a quiet and comfortable room, go to bed only when we are sleepy, avoid supine position during sleep and avoid chronic intake of sedative or hypnotic drugs (7). The following measures are indicated for all patients with SAHS (Table 3):

Table 3: Sleep hygiene recommendations (7)

- Go to bed only when you are sleepy.
- If you do not fall asleep within 20 minutes, get up and do something boring until you get sleepy.
- Do not make long naps.
- Try to go to bed always at the same time.
- Avoid intense exercise before bedtime.
- Use the bed only for sleep or sex. Avoid watching TV on the bedroom.
- Do not intake caffeine, nicotine or alcohol, or sedative drugs at least 6 hours before bedtime.
- Sleep in a quiet and comfortable room
- Try to sleep in a lateral position.
- Use sunlight and physical exercise to synchronize the circadian biological clock.
- Weight loss.

- Diet: If the patient has a BMI >25, it is very important to lose weight. A reduction of 10% of weight can improve AHI and the symptomatology (3).

- CPAP (continuous positive airway pressure):

  It is the most important treatment for SAHS and nowadays, it is the gold standard for its treatment. CPAP can improve daytime sleepiness, snoring, oxygen desaturation, arousals and attention capacity. It reduces the risk of crashes and normalizes blood pressure in hypertensive patients (3,24).

  Therefore, it is demonstrated that it is a very cost-effective treatment (7).

The indications of CPAP according to SEPAR guideline (3) are:

- If the patient has an AHI ≥ 30 per hour.
- If the patient has an AHI 5-30 plus symptoms and/or Epworth scale ≥12 and/or associated comorbidities.

It has little side effects, normally during the first week and they are mostly transitory. The most common ones are nasal congestion, epistaxis, skin irritation, conjunctivitis and rhinitis, due to the mask or pressure related (3).

- Mandibular advancement device:

Its efficacy is only demonstrated in the treatment of snoring and in mild and moderate SAHS with low BMI and not important desaturations. It can be useful in patients with upper airway resistance syndrome (entity characterized by sleepiness due to the occurrence of RERAS during sleep) and as a second line of treatment in patients who do not stand CPAP devices (3).

- Surgery:

It has demonstrated a limited efficacy in SAHS treatment and its types, indications and efficacy are under investigation (3).

2. Hypertension

1. Definition of hypertension

Hypertension is a very prevalent disease that affects about 16.9% of the general population older than 14 years (25):

Hypertension is defined as a persistent elevation of systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg in patients aged 18 or over (25,26). It is considered that blood pressure (BP) is persistently elevated when the average between two BP measures on the same day are elevated, in total of three consecutive visits.

We consider that there are different stages of severity. According to the Spanish consensus (25), they are (Table 4):

Table 4: HTN categories (25)

Categories	SBP (mmHg)	DBP (mmHg)
Optimal	<120	<80
Normal	120-129	80-84
Normal-high	130-139	85-89
Stage 1 hypertension	140-159	90-99
Stage 2 hypertension	160-179	100-109
Stage 3 hypertension	≥180	≥110

2. Hypertension management

According to the clinical guide of hypertension valid in Catalonia, the recommendations are (25):

- Initial study:

  We need to study if the patient has familiar antecedents of hypertension, cardiovascular disease, diabetes, dyslipidemia, neurofibromatosis, multiple endocrine neoplasia, or polycystic kidney disease. Also it is important to ask about personal antecedents:

  - Evolution time of hypertension, previous treatments, usual blood pressure of the patient, pregnancy and hypertensive crises.
  - Medication and drug intake.
  - Symptoms that orient toward a secondary cause of hypertension.

- Cardiovascular antecedents and cardiovascular risk factors (Aging, smoking, dyslipidemia, alteration of glucose, abdominal obesity and cardiovascular disease in first grade familiars).
- Non-healthy habits like alcohol consumption, drugs and sedentary lifestyle.

- Physical examination:
  - Blood pressure measurement.
  - Weight, height, abdominal perimeter and BMI.
  - Morphologic aspects: fat distribution.
  - Neck exploration: pulses, murmurs, and jugular stasis.
  - Cardiac exploration: rhythm, frequency, and murmurs.
  - Limbs exploration: pulses and edema.
  - Abdominal exploration: abdominal masses.
  - Ocular fundus if the patient suffers diabetes, grade 3 of hypertension or hypertensive emergencies.

- Complementary tests:
  - Blood and urine tests: glucose, uric acid, total cholesterol, HDL and LDL cholesterol, triglycerides, ionogram, creatinine, glomerular function, urine sediment and albumin/creatinine quotient.
  - Electrocardiogram.

3. Treatment of hypertension

All the patients diagnosed of hypertension would have to do some hygienic-dietetic measures to reduce the blood pressure and their cardiovascular risk. The most important ones are weight reduction, low salt intake and physical exercise (25).

The pharmacological treatment depends on blood pressure levels and the cardiovascular risk of the patient (25):

It is obligated to all the people who present values ≥ 180 SBP and/or ≥110 DBP, and for the people with cardiovascular disease or kidney disease.

It is recommended to all the people with stage 2 hypertension, and stage 1 with high risk (organ lesion, metabolic syndrome or ≥3 cardiovascular risk factors). For those people with stage 1 with moderate risk (1-2 cardiovascular risk factors associated), the pharmacological treatment will be indicated after 6 weeks of hygienic-dietetic measures without blood pressure normalization; and after 6 months for those people with type 1 without other cardiovascular risk factors.

3. Association between SAHS and hypertension

It is widely demonstrated that SAHS is associated with hypertension independently of confounding factors (5,6,27–30). Furthermore, there is a dose-response association, where mild to severe SAHS have approximately two and three times respectively the odds of having hypertension. And, in addition, even people with minimal sleep-disordered breathing have higher odds of hypertension (27).

Despite there are three cohort studies that confirm that SAHS can cause hypertension (27,31,32), there are two other community cohort studies that do not support this idea of causality (33,34). Therefore, for the moment, the causality relationship is unclear (29).

The prevalence of hypertension in patients with SAHS is 50-60% and it is related to severity. And, on the other side, 30-40% of hypertensive people also have SAHS (28,35), and this prevalence increase to 70% in those with drug resistant hypertension (29).

Pathophysiological mechanisms

During normal sleep, blood pressure tends to reduce its values up to 10-15% compared to wakefulness. This reduction is due to a sympathetic withdrawal during non-rapid eye movement (NREM) that causes lower BP, lower heart rate, lower cardiac output and lower systemic vascular resistance. By the contrary, during rapid eye movement (REM) there is an elevation of BP, heart rate and sympathetic nervous system. Considering that REM sleep lasts only approximately 20% of total sleep, the net effect on cardiovascular measures is still a reduction from awake levels (29).

On the other hand, in a patient with SAHS, there is an elevation of the sympathetic nervous system and heart rate during sleep due to the hypoxemia, hypercapnia, the large negative intrathoracic pressure and the arousals from sleep, caused by the respiratory events. All these effects activate some receptors that stimulate systemic vasoconstriction producing an increase of BP. Also, the arousals themselves produce tachycardia and a withdrawal of parasympathetic activity that promotes hypertension (6,29,36).

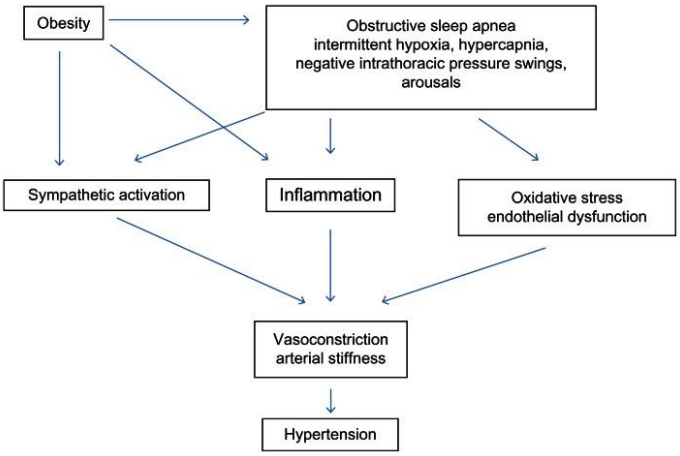


Figure 3: pathophysiological mechanisms (29)

4. JUSTIFICATION

As stated above, sleep apnea and hypopnea syndrome is a very prevalent disease and only 10% of the cases are correctly diagnosed (10,14), and untreated SAHS has associated significant medical costs (37) and fatal consequences for the patient (7,20).

There is large evidence that sleep apnea and hypopnea syndrome is associated with hypertension (3,5,6,27–30). Moreover, it is shown that undiagnosed SAHS is common among patients with hypertension in primary care (35).

Besides the presence of hypertension, patients with SAHS are more likely to suffer other cardiovascular diseases (3,6,15,16), metabolic syndrome (12), neurobehavioral consequences (6,12), traffic crashes (6,22) and it is an independent risk for all-cause mortality (19,21); which make the diagnosis of SAHS something essential.

At the moment, there is no evidence about the prevalence of SAHS in patients recently diagnosed of hypertension. All data come from studies that determine SAHS prevalence in long-term known hypertension or in the general population. Therefore, at present, it is still unknown how many patients suffer SAHS among those who have early hypertension diagnosis, and so less probability of vascular consequences, which would be more easily reversible, because of less time lapsed under that condition.

Consequently, knowing its prevalence can radically change the way that we manage hypertension, as nowadays it is still confusing how to manage this kind of patients. If we found a high sleep respiratory disorders prevalence among these patients, we would be able to propose strategies for SAHS diagnosis when a patient would be diagnosed of hypertension. As a result, with this early diagnose we would be able to avoid its multiple consequences, and so its mortality, with the right treatment (3,34).

5. HYPOTHESIS

Primary hypothesis

The prevalence of sleep apnea and hypopnea syndrome (SAHS) in patients recently diagnosed as having hypertension is higher than the prevalence of SAHS in the general population.

Secondary hypothesis

There is a relation between SAHS and hypertension severity in subjects recently diagnosed as having hypertension in primary care.

6. OBJECTIVES

Main objective

This study aims to quantify the prevalence of SAHS in patients who have been recently diagnosed as having hypertension (within the previous year) in primary care.

Secondary objective

The secondary objective is to analyze the prevalence of SAHS among the different stages of hypertension in patients recently diagnosed as having hypertension in primary care.

7. MATHERIAL AND METHODS

1. STUDY DESIGN

This study is designed as a cross-sectional study, analyzing the prevalence of SAHS in the population with recent diagnosis of hypertension.

The professionals of the primary care centers of Girona together with the sleep unit of the Respiratory Service of the Hospital Universitari Doctor Josep Trueta of Girona will perform the present study.

2. POPULATION

The participants of the study will be patients with recent diagnosis of hypertension (< 1 year) in the primary care centers of Girona, who will be selected from a computerized medical record "Estación clínica de atención primaria" (ECAP).

3. INCLUSION AND EXCLUSION CRITERIA

1. **Inclusion criteria**

- Patients aged 18- 65 years old.
- Patients with diagnosis of hypertension less than one year ago.
- Patients in treatment with pharmacological antihypertensive drugs.

2. **Exclusion criteria**

- BMI >40
- Neuromuscular pathology
- Severe heart disease with Fraction of Ejection of the left Ventricle (FEV) <50%
- Hypoxemia due to other causes different from SAHS (chronic respiratory diseases, cardiac diseases, thoracic cage disease, alveolar hypoventilation of all causes).
- Hypertension diagnosed without following the standard criteria from clinic guidelines.

4. SAMPLE

Sampling method

We will perform a stratified probabilistic sample method. We will select the patients who will participate in our study from a list of all the patients diagnosed of hypertension during last year in the primary care centers of Girona (ABS Girona 1: Santa Clara; ABS Girona 2: Can Gibert del Pla; ABS Girona 3: Montilivi and ABS Girona 4: Taialà). This list will be the "Estación clínica de atención primaria (ECAP)", which is a computerized medical record that all professionals from IAS (Institut d'Assistència Sanitària) and ICS (Institut Català de la Salut) use in Girona. This database has information for each patient diagnosis. We will search for patients with codes of primary hypertension (I10) and we will include patients with malignant hypertension (401.0), benign hypertension (401.1) and non-specified hypertension (401.9). If they meet the inclusion and exclusion criteria, they will be invited to participate. When we select a patient, we will contact him/her by phone. If he/she accepts participate in the study, we will give him/her the information document (*Annex 5*) and the informed consent (*Annex 6*).

We will stratify the sample by age (under or over 40 years old) and gender (male or female) in order to avoid confounding factors.

Sample size

As there is evidence that shows that a 2-4% (9) of the general population suffers symptomatic SAHS and between 30-40 % of people who has hypertension also have SAHS (28), we have estimated that a 20% in our population of recent hypertension would suffer SAHS.

With this hypothesis, we have calculated the sample size with the online application GRANMO. We have found that a sample size of 246 subjects randomly selected will suffice to estimate with a 95% confidence a precision +/- 5 percent units, a population percentage considered to be around 20%.

5. VARIABLES: METHODS OF MEASUREMENT

1. Main variable

Sleep apnea and hypopnea syndrome: Dichotomy Qualitative

We will measure the prevalence of SAHS with a respiratory poligraphy (PG) to all patients who meet the inclusion and exclusion criteria. The instrument we will use will be a portable recording device called ApneaLink© (Resmed, USA). It is a device that can diagnose SAHS in the comfort of the patient's home. It records respiratory effort, pulse, oxygen saturation and nasal flow during sleep. With this mechanism we will be able to record the apneas and hypopneas and then a physician specialized in sleep disorders will evaluate the results in Hospital Universitari Josep Trueta de Girona in the sleep unit next morning when they bring back the poligraphy.

Some authors opine that ApneaLink© is only validated for symptomatic patients with SAHS but it is useful when a polysomnography disponibility (PSG) is limited (38). Moreover, according to SEPAR 2011 guideline, PG is useful even when there are low probability pretest of SAHS diagnose, like in our case (3). As long as ApneaLink can slightly underdiagnose SAHS but is infrequent to overdiagnose it, it can be perfectly used to estimate the prevalence in this case because we want to demonstrate that SAHS is more prevalent than we thought. Therefore if we confirm our hypothesis it would not be a big problem the potential underdiagnose of Apnealink ©. Another advantage of ApneaLink © is that it is cheaper and more convenient than a PSG, so it makes the study affordable.

In those patients in whom there was SAHS symptoms according to diagnostic criteria of SEPAR 2011 guideline and PG does not confirm the presence of an AHI >5, a PSG will be performed in the Sleep Unit.

We will classify the patient in the group who suffer SAHS if he accomplishes SAHS definition, understand as having an AHI >5 plus symptoms or comorbidity not explained by other causes (3).

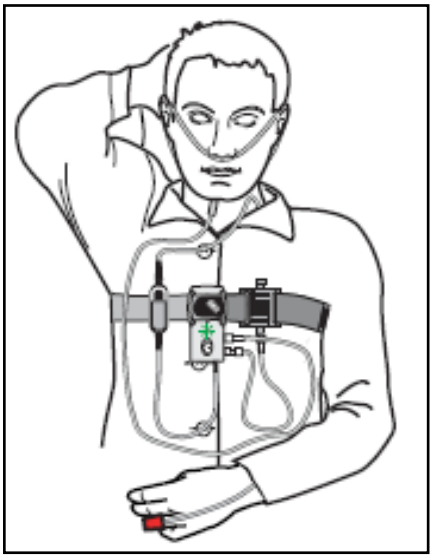


Figure 3: ApneaLink device

2. Covariates

We need to take these variables into account to interpret the outcomes. If we found significant differences, these covariates will be analyzed with a multivariate analysis. They are:

- Age: years. The prevalence of SAHS increase with age, it is one of the most important risk factors (3,5).
- Gender: male or female. It is known that males have more prevalence of SAHS than females in a relation of 2-3:1 in middle ages, although proportion tends to equilibrate after menopause (9).
- Smoking: non-smoking-, smoker, ex-smoker. Tobacco may increase the incidence of SAHS (3).
- Body mass index (BMI): kilos/metre^2. Obesity is one of the most important risk factors for SAHS (3).
- Neck circumference: Centimeters (Cm). Having a short and big neck is a risk factor for SAHS.
- Stress: We have to consider it due to stress causes elevation on blood pressure and can produce cofounding outcomes. Measured with the Perceived Stress Questionnaire (PSQ) (*Annex 2*) (39).
- Diabetes mellitus (DM): DM and SAHS are associated entities (3). We will diagnose DM following the American Diabetes Association recommendations (40) if it does not appear in the patient's clinical history.
- Cardiovascular risk factors: As SAHS is associated with cardiovascular comorbidities (15); we need to take into account the cardiovascular risk factors of each patient. It will be calculated with the REGICOR risk scale (*Annex 3*) (41).
- Stage of hypertension: A high grade of hypertension may indicate that it is a long-term evolution hypertension not diagnosed previously and it is useful to achieve our secondary objectives.
- Severity of SAHS: It is shown that people who suffer mild or severe SAHS have two or three times, respectively, the odds of having hypertension (27). It will be calculated with AHI.

Table 5: Covariates				
Variable	**Type of data**	**Categories or values**		**Measure instrument**
Sleep apnea hypopnea syndrome	Dichotomy Qualitative	- SAHS (AHI >5 plus symptoms or comorbidity not explained buy other causes) - No SAHS		ApneaLink poligraphy ©
Age	Discrete Quantitative	Number of years		ID card
Gender	Nominal Qualitative	- Male - Female		ID card
Smoking	Nominal Qualitative	- Non- smoker - Smoker - Ex- smoker		Anamnesis
Body mass index (BMI)	Ordinal Qualitative	- Normal weight: 18.5-25 - Overweight: 25-30 - Type 1 Obesity: 30-35 - Type 2 Obesity: 35-40 - Morbid obesity: >40		Relationship between weight and height: Kilos/metre^2
Neck circumference	Dichotomy Qualitative	Men: - >42 cm - < 42 cm	Women: - > 38 cm - < 38 cm	Centimeters (cm)
Stress	Ordinal Qualitative	- Very low stress: 0-7 - Low stress: 8-11 - Normal stress: 12-15 - High stress: 16-20 - Very high stress: ≥ 21		Measured with PSQ (*Annex 2*)
Diabetes mellitus (DM)	Dichotomy Qualitative	- DM - No DM		Diagnosed with DM criteria explained before.
Cardiovascular risk factors	Ordinal Qualitative	Low risk: <5% Moderate: 5-9% High risk: 10-14% Very high risk: ≥15%		Calculated with REGICOR risk tables (*Annex 3*)
Stages of hypertension	Ordinal Qualitative	- No HTN: < SBP 140/ DBP 90 - Stage 1: SBP 140-159/ DBP 90-99 - Stage 2: SBP 160-179/ DBP 100-109 - Stage 3: ≥ SBP 180/ DBP 110		It will be measured by a sphygmomanometer as explained before.
Severity of SAHS	Ordinal Qualitative	- AHI< 5 - AHI 5-15 - AHI 16-30 - AHI>30		ApneaLink poligraphy ©

6. DATA COLLECTION AND STUDY CIRCUIT

For data collection we will contact to the physicians working in the primary care centers of Girona. We will inform them about our study and we will ask for their collaboration in order to work together with the Sleep Unit in Hospital Doctor Josep Trueta in Girona for data collection.

The study circuit is described below:

A) Patient recruitment: The researchers will contact by phone patients previously selected from ECAP with recent diagnosis of hypertension in one of the primary care centers selected for the study who meet the inclusion and exclusion criteria. Researchers will ask them to participate in the study.

B) Primary care visit: When we have collected all the participants, the professionals of these primary care centers will visit the patients and will fill the data collection sheet (*Annex 4*) for each patient after they have read the information document (*Annex 5*) and signed the informed consent (*Annex 6*). They will confirm if the participants meet the inclusion and exclusion criteria.

C) Sleep Unit in Hospital Josep Trueta: The participants will be sent to the sleep unit in Hospital Josep Trueta, where we will give them the ApneaLink© device and we will teach them how to use it.

D) Participants in their homes: The participants selected will use ApneaLink© in their homes for one night and the next morning they will bring back the device to the Sleep Unit in Hospital Josep Trueta.

E) Sleep Unit in Hospital JosepTrueta: The sleep physicians specialists will analyze the data collected from ApneaLink the day before and will decide if the patient suffers SAHS or not according to the SEPAR normative (3). If PG is not concluding according to the diagnostic symptoms criteria of SEPAR 2011, a PSG will be performed in the next 2 weeks.

8. STATISTICAL ANALYSIS

1. Descriptive analysis

To calculate the prevalence of SAHS in patients with recent onset hypertension we will perform a descriptive analysis of the variables. The results for all the qualitative variables collected will be expressed as percentages for each group, while the continuous variables will be expressed as mean ± standard deviation if they were normally distributed and expressed as medians (quartiles) if they were not normally distributed.

2. Bivariate analysis

In order to analyze the prevalence of SAHS by severity groups we will perform a chi-square test (χ^2) due to our main variables (presence of SAHS and recent hypertension) are both qualitative ones. The Student's T test or Man-Whithney and ANOVA/ Kruskal-Wallis tests would be performed to compare 2 groups or ≥3 groups, respectively if we were comparing a qualitative and a quantitative variable.

3. Multivariate analysis

In order to avoid potential confounders and to give more external validity to our study, the analysis will be performed by a logistic regression to assess the association between the severity groups of SAHS and the severity groups of hypertension adjusted for the covariates, due to our main variables are both qualitative.

We will consider that there are a significant difference between groups when $p<0.05$. In these cases of significant statistics, the analysis will be adjusted for covariates.

9. ETHICAL CONSIDERATIONS

Our study will be performed according to the ethical principles for medical research established by the World Medical Association in the *Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects*. We will present the present protocol to the Clinical Research Ethical Committee (CEIC, "Comitè Ètic d'Investigació Clínica") at Hospital Universitari Doctor Josep Trueta in order to be evaluated and approved before starting the research.

According to "*Ley Orgánica 15/1999 de Protección de Datos de Carácter Personal*" and the "*Real decreto 1720/2007, de 21 de Diciembre, por el que se aprueba el reglamento de desarrollo de la ley orgánica 15/1999*", the clinical information used in the study of the participants will be confidential and only used for research. Also, we will work according to the *"Ley 14/2007, de 3 de Julio, de investigación biomédica*".

We will give an information document (*Annex 5*) to all the participants, and all the patients who will finally participate in the study will sign voluntarily the informed consent (*Annex 6*), and we will inform them how to use ApneaLink before the study starts.

The research team declares to have no conflicts of interest with any party or organ related to this study.

10. STRENGTHS AND LIMITATIONS

We have detected and took into account some limitations that interfere in the research. We explain below the most relevant ones:

- Our study is designed as a cross-sectional study so we will not be able to establish causality between recent hypertension and SAHS, we can only suggest the association between them. We cannot make assumptions about what factor precedes the other factor.

- Because of the fact that we will perform a stratified probabilistic sampling method, a possible selection bias will be avoided.

- In order to avoid another selection bias we have decided to include all the primary care centers of Girona for the sample recruitment. This gives us another advantage because each one of the primary care professionals who will collaborate with our study will have to visit fewer participants.

- When we measure the presence of SAHS, we will use PG instead of PSG because its price and its commodity for the patient. There can be an information bias because it is not the gold standard diagnostic method, but we will accept this small risk to carry on our research to make the study affordable and because SEPAR agreed that it can be used in situations like that. Notwithstanding, the risk will be minimized by performing in-hospital PSG in those dubious cases, according to SEPAR 2011 guideline (clinical suspecting with normal PG).

- Another information bias could be that our data collection comes from a database ECAP. This can produce that different professionals, not following the same recommendations, could diagnose patients differently. To avoid that, we will contact by phone all the professionals who participate in the study and make sure that they have accomplished the recommendations and the diagnostic criteria for hypertension.

- To avoid a possible confounding bias, we will perform a multivariate analysis, especially because the data of the patients is from a previous database so it is difficult to control possible confounding variables.

11. WORK PLAN

Stage 0: Study design: November 2015- January 2016

This stage is already done. We have done the bibliographic research and protocol design.

Stage 1: Ethical evaluation: February 2016

We will submit our protocol to the Clinical Research Ethical Committee (CEIC, "Comitè Ètic d'Investigació Clínica") at Hospital Universitari Doctor Josep Trueta de Girona for its approval.

Stage 2: Initial coordination: March 2016

We will do the first meeting with all the people involved with the study, including the primary health care workers together with professionals from the sleep unit in Hospital Josep Trueta. In this meeting we will clarify the different phases of the study with the chronogram and we will review the roles of each participant. The whole research team will keep in contact via e-mail and/or telephonic messages.

Stage 3: Patient recruitment: March 2016- May 2016

We will search on ECAP retrospectively all the patients diagnosed of hypertension during the last year (period from March 2015 to March 2016) and those selected who meet the inclusion and exclusion criteria they will be asked to participate in our study by phone.

Stage 4: Data collection: June 2016-November 2016

All the participants will have a visit with one of our primary care professionals for clinical examination and to fill the data collection sheet and the informed consent.

Also they will come to the sleep unit to take their poligraphy ApneaLink© during one night and the same sleep professionals will explain them how to use it and what to do. Next morning, the participants, will return the device and the sleep professionals will analyze the data collected.

Stage 5: Statistical analysis: November 2016- January 2017

A qualified statistician will process the data collected performing a descriptive analysis, bivariate and multivariate analysis.

Stage 6: Final article elaboration and publication of the results: January 2017- March 2017

The researchers of the group will do this and we will publish the article in different national and international medical journals in order to make a correct diffusion of the results.

12. STUDY CHRONOGRAM

Year	2015		2016												2017		
Month	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M
Stage 0: Study design																	
Stage 1: Ethical evaluation																	
Stage 2: Initial coordination																	
Stage 3: Patient recruitment																	
Stage 4: Data collection																	
Stage 5: Statistical analysis																	
Stage 6: Final article and publication																	

13. BUDGET

Expenses		**Cost**
1. **Personnel expenses**		0€
2. **Executive expenses**		
	ApneaLink poligraphy: 2x batteries (5€) 1x Cannula (15€) Depreciation of equipment (20€) Sleep professional to analyze the poligraphy (x1h, per 30€/h) Nursery to install the equipment (x45 min, per 20€)	90€ x 246 patients= 22.140€
	Statistical Analysis (x25h, per 35€/h)	875 €
3. **Publication and dissemination expenses**		
	Scientific publication	1000 €
	Attendance to scientific meetings and congress	1000 €
TOTAL		25.015€

14. CLINICAL AND HEALTH CARE IMPACT

This study can radically change the way that we manage hypertension in primary care. If our hypothesis is confirmed, we would be able to propose solutions for SAHS underdiagnose in this population and avoid its fatal consequences.

For example, in order to decrease the SAHS underdiagnose, we can suggest the creation of a protocol that recommends a screening questionnaire for SAHS to all the people who was diagnosed of hypertension; or, moreover, we can recommend doing a standardized poligraphy to this population, if the incidence is really important.

In addition of the objectives of the project, we will also be able to identify some clinical characteristics of the patients with a recent diagnosis of hypertension with or without SAHS (such as symptoms of SAHS, age, gender, BMI, smoking, stress, DM and cardiovascular risk factors) which are, in fact, the covariates of the study, and which can help us to define those patients with more risk of SAHS.

Finally, this study can help with public health costs because, improving SAHS diagnose and, therefore, improving SAHS treatment, we will be able to reduce medical costs and morbi-mortality in this huge group of patients.

15. BIBLIOGRAPHY

1. American Academy of Sleep Medicine. International classification of sleep disorders, revised: Diagnostic and coding manual. Chicago, Illinois. American Academy of Sleep Medicine; 2001.
2. American Academy of Sleep Medicine Task Force. Sleep – Related Breathing Disorders in Adults : Recommendations for Syndrome Definition and Measurement Techniques in Clinical Research. Sleep. 1999;22(5):667–89.
3. Lloberes P, Durán-Cantolla J, Ángel Martínez-García M, Marín JM, Ferrer A, Corral J, et al. Diagnóstico y tratamiento del síndrome de apneas-hipopneas del sueño. Arch Bronconeumol [Internet]. 2011 [cited 2015 Nov 6];47(3):143–56. Available from: http://www.archbronconeumol.org/es/diagnostico-tratamiento-del-sindrome-apneas-hipopneas/articulo/S0300289611000238/
4. Consenso Nacional sobre el Síndrome de Apneas- Hipopneas del sueño. Arch Bronconeumol. 2005;41(4):81–101.
5. Durán J, Esnaola S, Rubio R, Iztueta Á. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med. 2001;163(3 I):685–9.
6. Young T, Peppard PE, Gottlieb DJ. Epidemiology of Obstructive Sleep Apnea. Am J Respir Crit Care Med. 2002;165(9):1217–39.
7. Durán-Cantolla J, Martínez-García MÁ. Apnea del Sueño en Atención Primaria Puntos clave. Sociedad Española de Neumología y Cirugía Torácica SEPAR; 2009. 13-122 p.
8. Epstein LJ, Kristo D, Strollo PJ, Friedman N, Malhotra A, Patil SP, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Cinical Sleep Med. 2009;5(3):263–76.
9. Young T, Palta M, Dempsey J, Skatrud J, Weber S BS. The occurrence of sleep disordered breathing in middle-aged adults. New Engl J Med. 1993;328:1230–5.
10. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol [Internet]. 2013 [cited 2015 Nov 15];177(9):1006–14. Available from: http://aje.oxfordjournals.org/content/177/9/1006
11. Chiner E, Arriero J, Signes Costa J, Marco J, Fuentes I. Validación de la versión española del test de somnolencia de Epworth en pacientes con síndrome de apnea del sueño. Arch Bronconeumol [Internet]. 1999 [cited 2015 Dec 6];35(9):422–7. Available from: http://dx.doi.org/10.1016/S0300-2896(15)30037-5
12. Simonds AK, De Backer W. Respiratory conditions. In: Respiratory Sleep Medicine ERS Handbook. Sheffield: European Respiratory Society; 2012. p. 21–38.
13. Shayeb M El, Topfer LA, Stafinski T, Pawluk L, Menon D. Diagnostic accuracy of level 3 portable sleep tests versus level 1 polysomnography for sleep-disordered breathing: A systematic review and meta-analysis. CMAJ. 2014;186(1):25–51.
14. Young T, Evans L, Finn L, Palta M. Estimation of the Clinically Diagnosed Proportion of Sleep Apnea Syndrome in Middle-aged Men and Women. Sleep. 1997;20(9):705–6.
15. Marin Jose M, Carrizo Santiago J, Vicente Eugenio, Agusti Alvar GN. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365:1046–53.
16. Sánchez de la Torre M, Campos-Rodriguez F, Barbé F. Obstructive sleep apnoea and

cardiovascular disease. Lancet Respir Med. 2013;1(1):61–72.

17. Costa C, Santos B, Severino D, Cabanelas N, Peres M, Monteiro I, et al. Obstructive sleep apnea syndrome: An important piece in the puzzle of cardiovascular risk factors. Clin Investig Arterioscler. Sociedad Española de Arteriosclerosis; 2014;27(5):256–63.

18. Alonso-Fernandez A, de la Pena M, Romero D, Pierola J, Carrera M, Barcelo A, et al. Association Between Obstructive Sleep Apnea and Pulmonary Embolism. Mayo Clin Proc [Internet]. 2013 [cited 2015 Dec 23];88(6):579–87. Available from: http://www.sciencedirect.com/science/article/pii/S0025619613001250

19. Marshall NS, Wong KKH, Liu PY, Cullen SRJ, Knuiman MW, Grunstein RR. Sleep Apnea as an Independent Risk Factor for All-Cause Mortality: The Busselton Health Study. Sleep [Internet]. 2008 [cited 2015 Nov 19];3131(88):1079–85. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2542953/

20. Fonseca MIP, Pereira T, Caseiro P. Death and Disability in Patients with Sleep Apnea - A Meta-analysis. Arq Bras Cardiol [Internet]. 2015 [cited 2015 Dec 10];58–65. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4387612/

21. Kendzerska T, Mollayeva T, Gershon AS, Leung RS, Hawker G, Tomlinson G. Untreated obstructive sleep apnea and the risk for serious long-term adverse outcomes: A systematic review. Sleep Med Rev [Internet]. 2014 [cited 2015 Dec 5];18(1):49–59. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23642349

22. Tregear S, Reston J, Schoelles K, Phillips B. Obstructive sleep apnea and risk of motor vehicle crash: systematic review and meta-analysis. J Clin Sleep Med. 2009;5:573–81.

23. Martínez-García MA, Campos-Rodriguez F, Durán-Cantolla J, de la Peña M, Masdeu MJ, González M, et al. Obstructive sleep apnea is associated with cancer mortality in younger patients. Sleep Med [Internet]. 2014 [cited 2015 Nov 20];15(7):742–8. Available from: http://linkinghub.elsevier.com/retrieve/pii/S138994571400094X

24. Durán-Cantolla J, Aizpuru F, Martínez-Null C, Barbé-Illa F. Obstructive sleep apnea/hypopnea and systemic hypertension. Sleep Med Rev. 2009;13:323–31.

25. Coll, G; Dalfó, A; Figuera, M; Gibert, E; Isnard, M; Martinez M. Guies de pràctica clínica: Hipertensió Arterial [Internet]. Barcelona: Institut Català de la Salut; 2012 [cited 2015 Nov 28]. p. 109. Available from: http://www.gencat.cat/ics/professionals/guies/docs/guia_hta.pdf

26. De la Sierra A, Gorostidi M, Marín R, Redón J, Banegas JR. Evaluación y tratamiento de la hipertensión arterial en España. Med Clin. 2008;131(3):104–16.

27. Peppard PE, Young T, Palta M, Skatrud J. Prospective Study of the Association Between Sleep-Disordered breathing and hypertension. N Engl J Med [Internet]. 2000 [cited 2015 Nov 8];342. Available from: http://www.nejm.org/doi/full/10.1056/NEJM200005113421901

28. Chahal C, Somers V. Secondary hypertension. Am Soc Hypertens [Internet]. 2015 [cited 2015 Nov 20];9(3):244–7. Available from: http://dx.doi.org/10.1016/j.jash.2015.02.001

29. Phillips CL, O'Driscoll DM. Hypertension and obstructive sleep apnea. Nat Sci Sleep [Internet]. 2013 [cited 2015 Nov 15];5(4):43–52. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3666153/

30. Nieto FJ, Young TB, Lind BK, Redline S, Agostino RBD, Newman AB, et al. Association of Sleep-Disordered Breathing, Sleep Apnea, and Hypertension in a Large Community-Based Study for the Sleep Heart Health Study. JAMA. 2000;284(14).

31. Marin M, Forner M, Carrizo SJ. Association between treated and Untreated Obstructive Sleep

Apnea and Risk of Hypertension. JAMA [Internet]. 2012 [cited 2015 Dec 3];307(20):1–3. Available from: http://211.144.68.84:9998/91keshi/Public/File/40/307-20/pdf/joc120004_2169_2176.pdf

32. Hla KM, Young T, Finn L, Peppard PE, Szklo-Coxe M, Stubbs M. Longitudinal association of sleep-disordered breathing and nondipping of nocturnal blood pressure in the Wisconsin Sleep Cohort Study. Sleep. 2008;31(6):795–800.

33. O'Connor GT, Caffo B, Newman AB, Quan SF, Rapoport DM, Redline S, et al. Prospective Study of Sleep-disordered Breathing and Hypertension. Am J Respir Crit Care Med [Internet]. 2009 [cited 2015 Dec 15];179(12):1159–64. Available from: http://www.atsjournals.org/doi/abs/10.1164/rccm.200712-1809OC

34. Cano-Pumarega I, Duran-Cantolla J, Aizpuru F, Miranda-Serrano E, Rubio R, Martinez-Null C, et al. Obstructive Sleep Apnea and Systemic Hypertension: Longitudinal Study in the General Population: the Vitoria Sleep Cohort. Am J Respir Crit Care Med [Internet]. 2011 [cited 2015 Dec 15];184(11):1299–304. Available from: http://www.atsjournals.org/doi/pdf/10.1164/rccm.201101-0130OC

35. Broström A, Sunnergren O, Årestedt K, Johansson P, Ulander M, Riegel B, et al. Factors associated with undiagnosed obstructive sleep apnoea in hypertensive primary care patients. Scand J Prim Health Care [Internet]. 2012 [cited 2015 Dec 7];30(2):107–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22643156

36. Konecny T, Kara T, Somers VK. Obstructive Sleep Apnea and Hypertension: An Update. Hypertension [Internet]. 2014 [cited 2016 Nov 26];63(2):203–9. Available from: http://hyper.ahajournals.org/cgi/doi/10.1161/HYPERTENSIONAHA.113.00613

37. Kapur V, Blough DK, Sandblom RE, Hert R, de Maine JB, Sullivan SD, et al. The medical cost of undiagnosed sleep apnea. Sleep. 1999;22(6):749–55.

38. Ng SSS, Chan TO, To KW, Ngai J, Tung a., Ko FWS, et al. Validation of a portable recording device (ApneaLink) for identifying patients with suspected obstructive sleep apnoea syndrome. Intern Med J. 2009;39(11):757–62.

39. Sanz-Carrillo C, García-Campayo J, Rubio a, Santed M., Montoro M. Validation of the Spanish version of the Perceived Stress Questionnaire. J Psychosom Res. 2002;52(3):167–72.

40. Iglesias R, Barutell L. Resumen de las recomendaciones de la American Diabetes Association (ADA) 2014 para la práctica clínica en el manejo de la diabetes mellitus. Diabetes Práctica; 05(Supl Extr 2). 2014;1–24.

41. Regicor. Taules per al càlcul del Risc Coronari [Internet]. Girona: Regicor; 2012 [cited 2015 Dec 21]. Available from: http://www.regicor.org/media/upload//arxius/quisom/framingham/Taules 2012 catala.pdf

16. ANNEXES

ANNEX 1: Epworth scale

VERSIÓN ESPAÑOLA DEL EPWORTH SLEEPINESS SCALE

¿Con qué facilidad da usted cabezadas o se queda dormido en las situaciones siguientes, a diferencia de encontrarse solamente cansado? Esto se refiere al tipo de vida que lleva últimamente. Aunque no haya realizado este tipo de cosas recientemente, trate de imaginar cómo le habrían afectado. Use la escala siguiente y elija el número más adecuado para cada situación.

0= Nunca me duermo

1= Ligeras posibilidades de dormir

2= Moderadas posibilidades de dormir

3= Altas posibilidades de dormir

Situación	**Posibilidades de dormir**
Sentado leyendo un periódico, una revista, un libro	
Viendo la televisión	
Sentado sin hacer nada en un lugar público (por ejemplo, un cine, una reunión familiar, una ceremonia religiosa)	
De pasajero en un coche al cabo de una hora sin parar	
Acostado tranquilo por la tarde cuando las circunstancias lo permiten	
Sentado hablando con alguien	
Sentado tranquilo después de una comida sin alcohol	
En un coche, si se para unos minutos por el tráfico	

ANNEX 2: Perceived stress questionnaire Spanish version (PSQ)

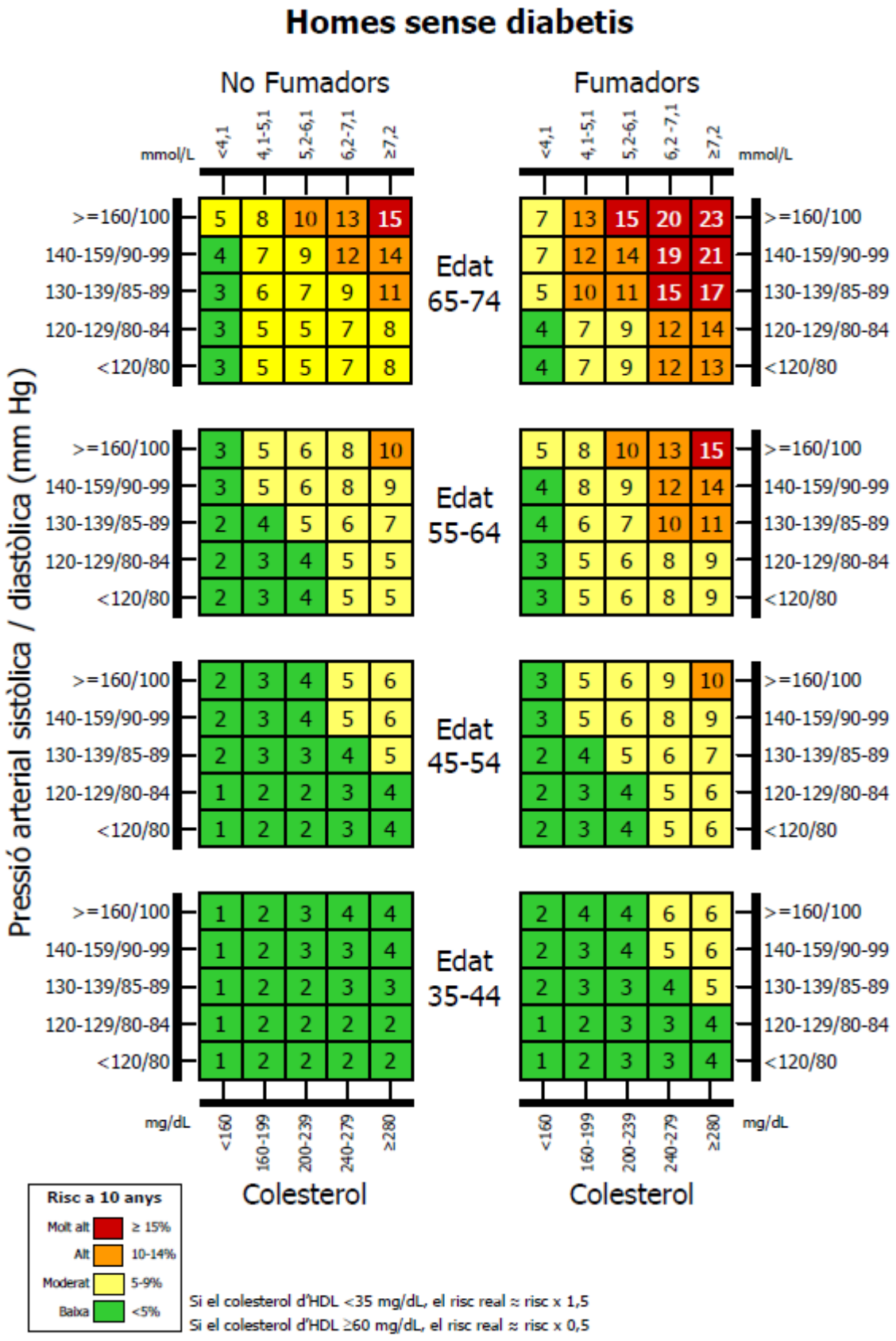
Las preguntas en esta escala hacen referencia a sus sentimientos y pensamientos durante el **último mes**. En cada caso, por favor indique con una "X" cómo usted se ha sentido o ha pensado en cada situación.

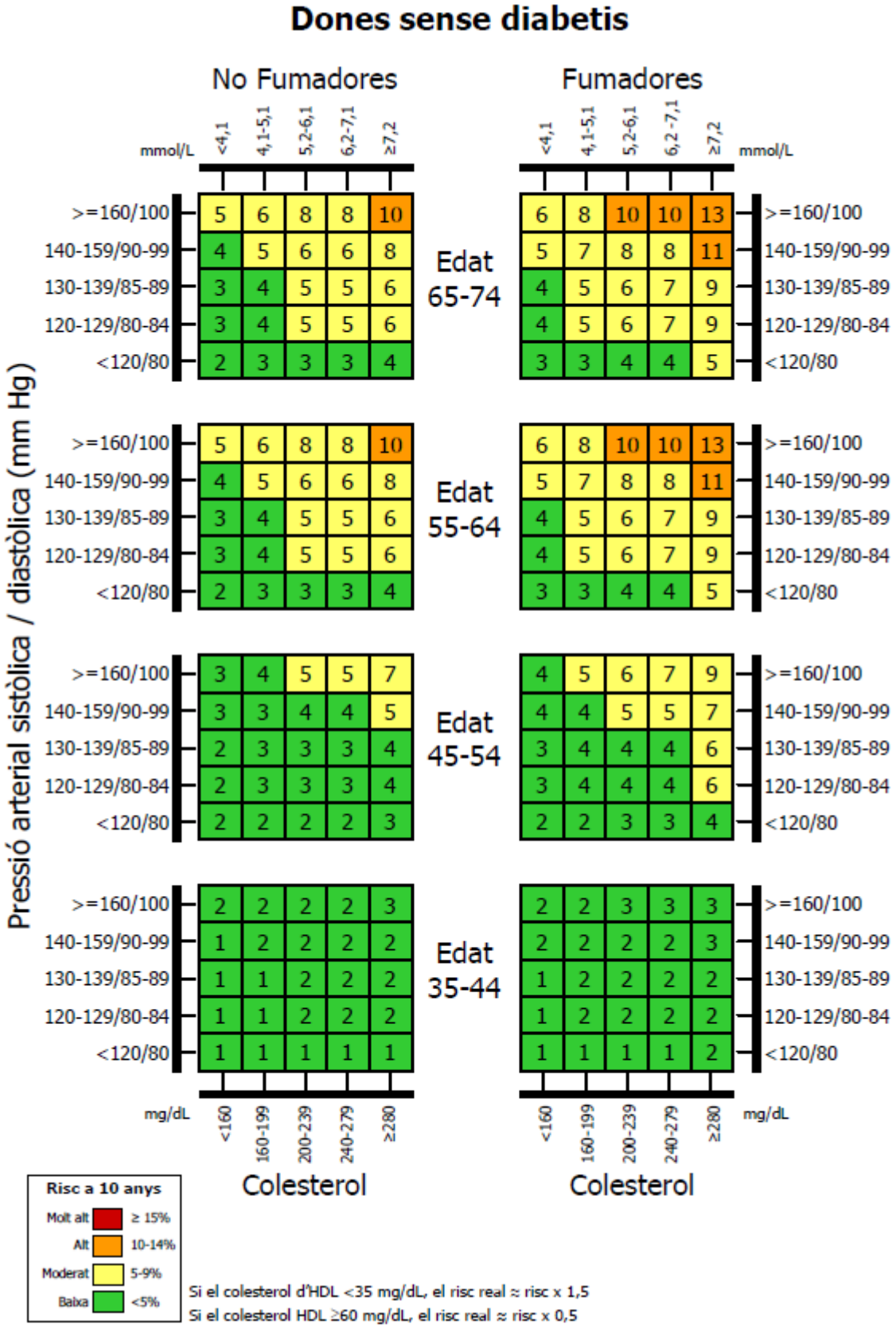
	Nunca	Casi nunca	De vez en cuando	A menudo	Muy a menudo
1. En el último mes, ¿con qué frecuencia ha estado afectado por algo que ha ocurrido inesperadamente?	0	1	2	3	4
2. En el último mes, ¿con qué frecuencia se ha sentido incapaz de controlar las cosas importantes en su vida?	0	1	2	3	4
3. En el último mes, ¿con qué frecuencia se ha sentido nervioso o estresado?	0	1	2	3	4
4. En el último mes, ¿con qué frecuencia ha manejado con éxito los pequeños problemas irritantes de la vida?	0	1	2	3	4
5. En el último mes, ¿con qué frecuencia ha sentido que ha afrontado efectivamente los cambios importantes que han estado ocurriendo en su vida?	0	1	2	3	4
6. En el último mes, ¿con qué frecuencia ha estado seguro sobre su capacidad para manejar sus problemas personales?	0	1	2	3	4
7. En el último mes, ¿con qué frecuencia ha sentido que las cosas le van bien?	0	1	2	3	4
8. En el último mes, ¿con qué frecuencia ha sentido que no podía afrontar todas las cosas que tenía que hacer?	0	1	2	3	4
9. En el último mes, ¿con qué frecuencia ha podido controlar las dificultades de su vida?	0	1	2	3	4
10. En el último mes, ¿con que frecuencia se ha sentido que tenía todo bajo control?	0	1	2	3	4

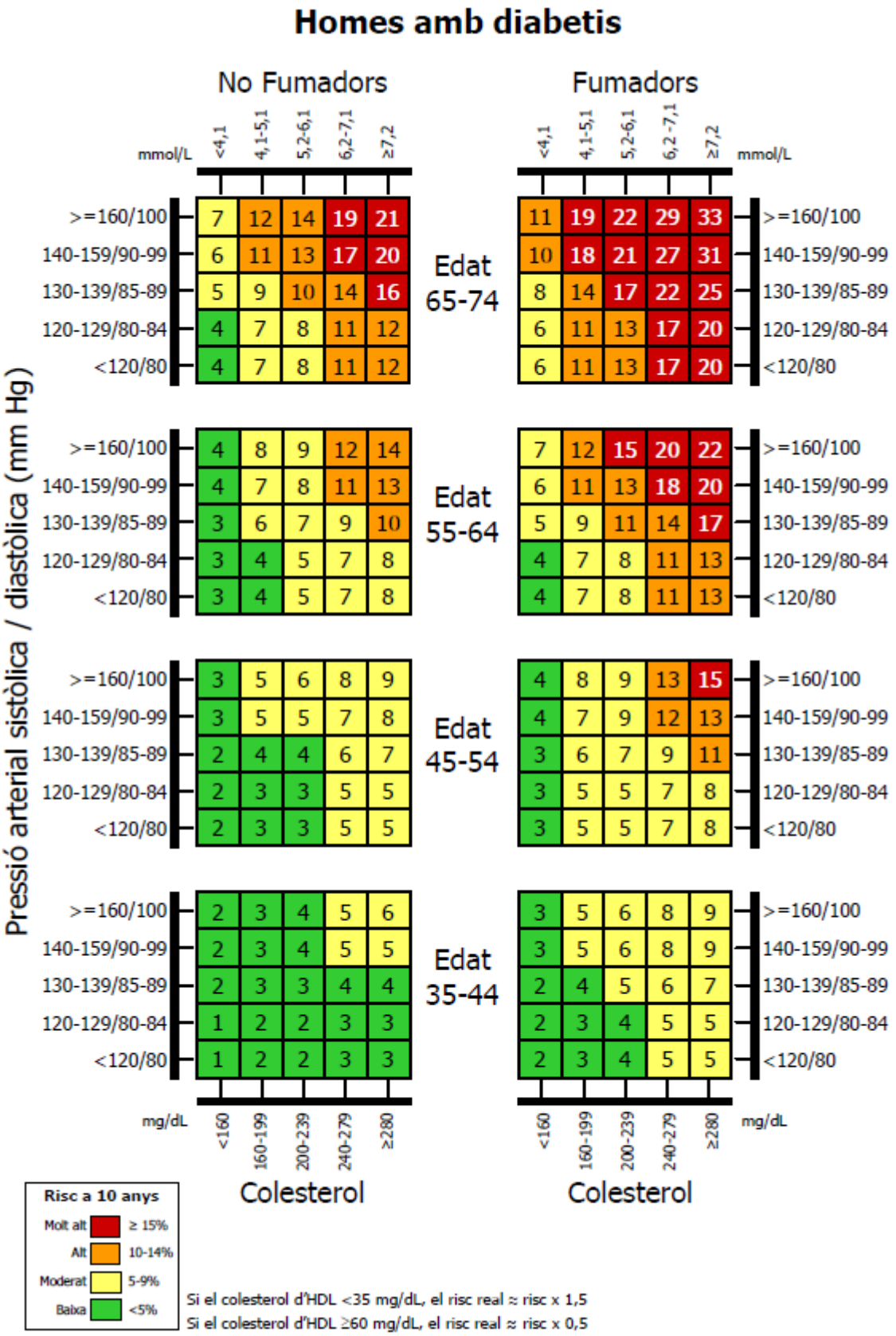
11. En el último mes, ¿con qué frecuencia ha estado enfadado porque las cosas que le han ocurrido estaban fuera de su control?	0	1	2	3	4
12. En el último mes, ¿con qué frecuencia ha pensado sobre las cosas que le quedan por hacer?	0	1	2	3	4
13. En el último mes, ¿con qué frecuencia ha podido controlar la forma de pasar el tiempo?	0	1	2	3	4
14. En el último mes, ¿con qué frecuencia ha sentido que las dificultades se acumulan tanto que no puede superarlas?	0	1	2	3	4

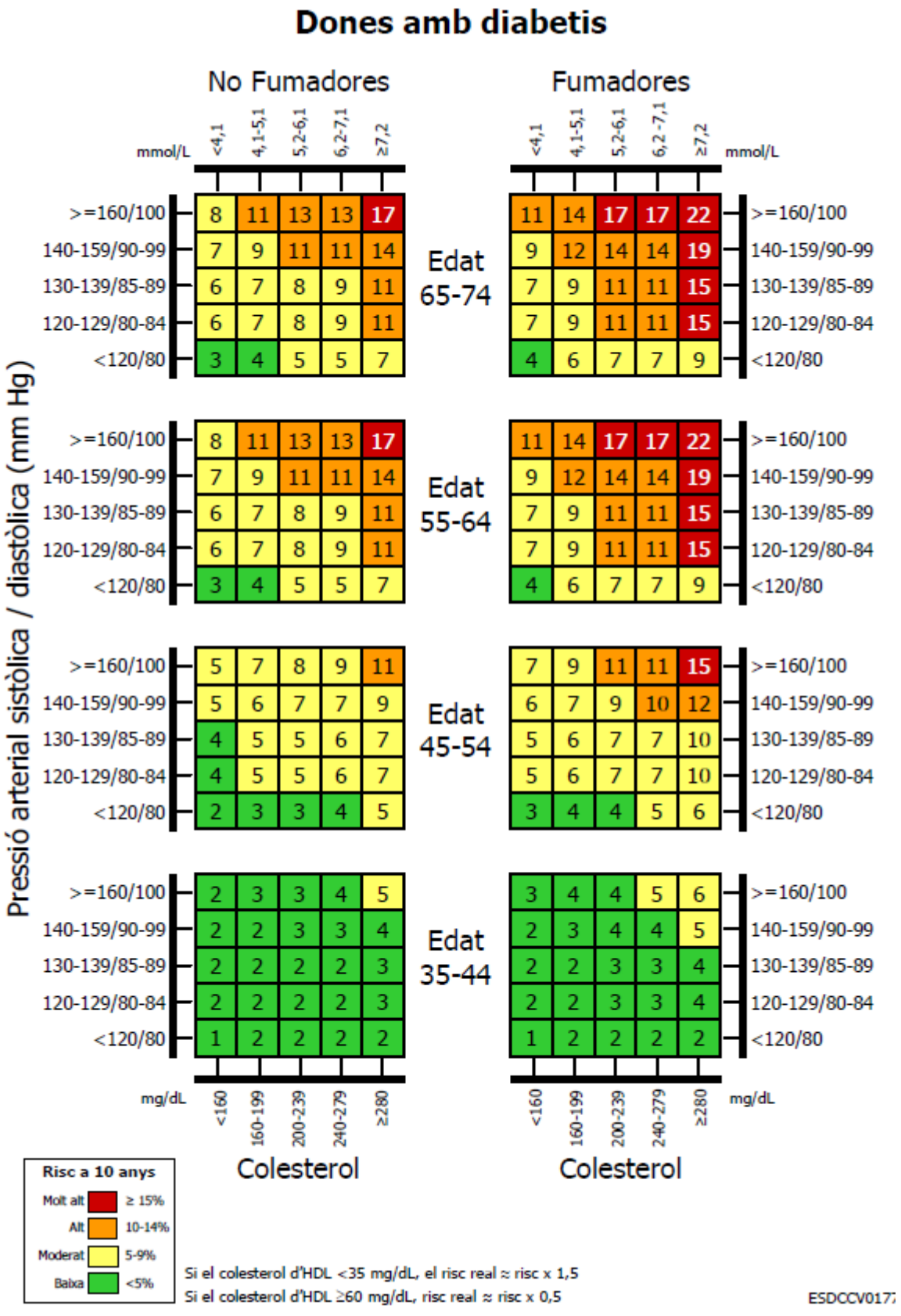
Esta escala es un instrumento de auto informe que evalúa el nivel de estrés percibido durante el último mes, consta de 14 ítems con un formato de respuesta de una escala de cinco puntos (0 = nunca, 1 = casi nunca, 2 =de vez en cuando, 3 = a menudo, 4 = muy a menudo). La puntuación total de la PSS se obtiene invirtiendo las puntuaciones de los ítems 4, 5, 6, 7, 9, 10 y 13 (en el sentido siguiente: 0=4, 1=3, 2=2, 3=1 y 4=0) y sumando entonces los 14 ítems. La puntuación directa obtenida indica que a una mayor puntuación corresponde un mayor nivel de estrés percibido.

ANNEX 3: REGICOR scale




Dones sense diabetis
No Fumadores
Fumadores
mmol/L
<4,1
4,1-5,1
5,2-6,1
6,2-7,1
≥7,2
6,2 -7,1
Pressió arterial sistòlica / diastòlica (mm Hg)
>=160/100
140-159/90-99
130-139/85-89
120-129/80-84
<120/80
Edat 65-74
Edat 55-64
Edat 45-54
Edat 35-44
5 6 8 8 10
4 5 6 6 8
3 4 5 5 6
3 4 5 5 6
2 3 3 3 4
6 8 10 10 13
5 7 8 8 11
4 5 6 7 9
4 5 6 7 9
3 3 4 4 5
3 4 5 5 7
3 3 4 4 5
2 3 3 3 4
2 3 3 3 4
2 2 2 2 3
4 5 6 7 9
4 4 5 5 7
3 4 4 4 6
3 4 4 4 6
2 2 3 3 4
2 2 2 2 3
1 2 2 2 2
1 1 2 2 2
1 1 2 2 2
1 1 1 1 1
2 2 3 3 3
2 2 2 2 3
1 2 2 2 2
1 2 2 2 2
1 1 1 1 2
mg/dL
<160
160-199
200-239
240-279
≥280
Colesterol
Risc a 10 anys
Molt alt
≥ 15%
Alt
10-14%
Moderat
5-9%
Baixa
<5%
Si el colesterol d'HDL <35 mg/dL, el risc real ≈ risc x 1,5
Si el colesterol HDL ≥60 mg/dL, el risc real ≈ risc x 0,5


Homes amb diabetis
No Fumadors
Fumadors
mmol/L
<4,1
4,1-5,1
5,2-6,1
6,2-7,1
≥7,2
6,2 -7,1
>=160/100
140-159/90-99
130-139/85-89
120-129/80-84
<120/80
Edat 65-74
Edat 55-64
Edat 45-54
Edat 35-44
Pressió arterial sistòlica / diastòlica (mm Hg)
mg/dL
<160
160-199
200-239
240-279
≥280
Colesterol
Risc a 10 anys
Molt alt ≥ 15%
Alt 10-14%
Moderat 5-9%
Baixa <5%
Si el colesterol d'HDL <35 mg/dL, el risc real ≈ risc x 1,5
Si el colesterol d'HDL ≥60 mg/dL, el risc real ≈ risc x 0,5


Dones amb diabetis
No Fumadores
Fumadores
mmol/L
<4,1
4,1-5,1
5,2-6,1
6,2-7,1
≥7,2
>=160/100
140-159/90-99
130-139/85-89
120-129/80-84
<120/80
Edat 65-74
Edat 55-64
Edat 45-54
Edat 35-44
Pressió arterial sistòlica / diastòlica (mm Hg)
mg/dL
<160
160-199
200-239
240-279
≥280
Colesterol
Risc a 10 anys
Molt alt ≥ 15%
Alt 10-14%
Moderat 5-9%
Baixa <5%
Si el colesterol d'HDL <35 mg/dL, el risc real ≈ risc x 1,5
Si el colesterol d'HDL ≥60 mg/dL, risc real ≈ risc x 0,5
ESDCCV0177

ANNEX 4: Data collection sheet

PARTICIPANT CODE:

- Age (years):_____
- Gender: Male ☐ Female ☐
- Height (cm) : _____ Weight (Kg): _____
- BMI: _____
  - ☐ Normal weight: 18.5-25
  - ☐ Overweight: 25-30
  - ☐ Type 1 Obesity: 30-35
  - ☐ Type 2 Obesity: 35-40
  - ☐ Morbid obesity: >40
- Smoking:
  - ☐ Non- smoker
  - ☐ Smoker
  - ☐ Ex- smoker
- Diabetes: ☐ Yes ☐ No
- Cardiovascular risk factors (REGICOR):
  - ☐ Low risk: <5%
  - ☐ Moderate: 5-9%
  - ☐ High risk: 10-14%
  - ☐ Very high risk: ≥15%
- Stages of hypertension:
  - ☐ Stage 1: SBP 140-159/ DBP 90-99
  - ☐ Stage 2: SBP 160-179/ DBP 100-109
  - ☐ Stage 3: ≥ SBP 180/ DBP 110
- Severity of SAHS:
  - ☐ AHI <5 ☐ AHI 16-30
  - ☐ AHI 5-15 ☐ AHI >30
- Neck circumference

  Men:
  - ☐ Normal: <42 cm
  - ☐ High: >42 cm

  Women:
  - ☐ Normal: <38 cm
  - ☐ High: >38 cm
- SAHS symptoms:
  - ☐ Excessive daytime sleepiness
  - ☐ Nocturnal choking
  - ☐ Frequent awakenings
  - ☐ Non refreshing sleep
  - ☐ Fatigue during the day
  - ☐ Concentrating difficulties
- PSQ: ☐ Very low 0-7 ☐ Low 8-11 ☐ Normal 12-15 ☐ High 16-20 ☐ Very high ≥21

ANNEX 5: Information document

FULL D'INFORMACIÓ PEL PARTICPIANT:

1. Generalitats:

El present estudi es durà a terme pel servei de Pneumologia de l'Hospital Universitari Josep Trueta de Girona, juntament amb els Centres d'Atenció Primària de Girona durant els mesos març 2016- març 2017.El projecte de recerca ha estat valorat i aprovat pel Comitè Ètic d'Investigació Clínica de l'Hospital Doctor Josep Trueta. Els participants de l'estudi hauran de sotmetre's a una poligrafia respiratòria (ApneaLink©).

2. Objectius i finalitat de l'estudi:

Amb aquest estudi es pretén calcular la prevalença de Síndrome d'Apnea i Hipoapnea de la Son (SAHS) en persones que s'hagin diagnosticat de hipertensió arterial en l'últim any a l'atenció primària i que prenguin tractament farmacològic antihipertensiu.

3. Participació:

La seva participació en l'estudi és totalment voluntària. El participant és lliure d'abandonar l'estudi si així ho desitja en qualsevol moment, sense necessitat de justificacions i sense que aquest fet afecti la seva assistència sanitària. La participació en l'estudi és totalment gratuïta i no s'obtindrà cap compensació econòmica per la participació.

4. Confidencialitat i protecció de dades:

S'adoptaran les mesures per garantir la confidencialitat de les seves dades en compliment de la *Llei Orgànica* 15/1999 i les dades recollides seran gestionades de forma anònima i només utilitzades amb fins d'investigació. També es garantiran els principis establerts per la *Llei d'Investigació Biomèdica* 14/2007.

5. Tasca del participant en la recollida de dades

El participant haurà de fer una visita en el seu CAP per tal de recollir dades per l'estudi i presentar-se a la unitat de Son de la 4a planta de l'Hospital Josep Trueta de Girona a on se li facilitarà un aparell d'Apnealink© amb el qual haurà de dormir una nit en el seu domicili. L'endemà al matí haurà de retornar-lo a la mateixa unitat a on s'analitzaran les dades obtingudes.

6. Resultats i beneficis per a la investigació:

El pacient està en el seu dret de ser informat dels resultats de la investigació, així i com es respectarà la seva voluntat de no ser informat respecte aquests. Els beneficis derivats de la investigació, tan poden beneficiar al participant com a altres persones, i aquests seran adequadament utilitzats per assolir els objectius de l'estudi i serviran de base per futures investigacions en aquest àmbit.

Gràcies per la seva participació.

ANNEX 6: Informed Consent

CONSENTIMENT INFORMAT

Declaració del participant:
Jo, _____

- He llegit la fulla informativa sobre l'estudi que se m'ha entregat.
- He pogut fer totes les preguntes necessàries respecte l'estudi.
- He rebut suficient informació sobre l'estudi.
- He estat informat per l'investigador _____ de les implicacions i finalitats de l'estudi.
- Entenc que la meva participació és voluntària.
- Entenc que es consultarà la informació relacionada amb aquest estudi del meu historial clínic.
- Entenc que puc revocar el meu consentiment de participació a l'estudi en qualsevol moment i sol·licitar l'eliminació de les meves dades personals sense cap repercussió en l'assistència sanitària posterior.
- He estat informat de que les dades obtingudes tenen com a objectiu la investigació biomèdica i que se'n respectarà la llei a tal efecte (14/2007).
- He estat informat de que està garantit el compliment de la llei de protecció de dades (15/1999).
- Accepto que els investigadors principals del projecte puguin contactar amb mi si en un futur es considera oportú?

Sí ☐ No ☐

Signatura del participant:	Signatura de l'investigador:
Data: ___ / ___ / _____	Data: ___ / ___ / _____