Acknowledgments

I want to begin with a sentence that describes this Master’s degree for me: “Happy people remember the past with gratitude, rejoice in the present and face the future without fear.” – Epicuro.

I have to say that I desired to attend this Master’s degree even when I was in my second year of graduation. In that year (2010) I went to a lecture with several of my current teachers and I realized that this area would be a great, or better said, the best way to go ahead in life.

I will remember everything of these two years. My colleagues, the teachers, the secretary (Patrícia), the people in the CINTESIS and CIDES department. They have really helped me to achieve what I’ve always wanted: to have a Master’s degree!

First, I want to thank myself. For all my effort, for surviving the adversities, for saying no to the impossible. I’ve always believed in myself, but to finish this, after all that I went through this last year, is really a way of proving to myself who I am.

Secondly, I want to thank my parents and brother. They are my foundation and the people that never give up on me. Even when I try to say that I cannot make it, they forbid me of doing that.

Thirdly, to Pedro Pereira Rodrigues, my teacher and mentor. I have to say that you’ve always backed me up. You’ve always trusted my work and me. I really appreciate all that you did for me and thanks for keeping believing in me. For me, you are not the “feared teacher” but the best teacher. I hope that our friendship continues.

Finally, to the Sleep Laboratory team of Vila Nova de Gaia/Espinho Hospital Center, especially Liliana Leite, and the Informatics Department in the name of Eng. Domingos Pereira and Eng. Joaquim Pereira. Without them I wouldn’t be allowed to collect the data.
Abstract

Introduction: In Obstructive Sleep Apnea, respiratory effort is maintained but ventilation decreases or disappears because of the partial or total occlusion in the upper airway. It affects about 4% of men and 2% of women in the world population. The major risk factors include obesity, advanced age and male sex. Diagnostic is based in signs and symptoms during a sleep testing – polysomnography.

Aim: To define a new auxiliary diagnostic method that can support the decision to perform polysomnography, based on signs and symptoms, prioritizing patients.

Methods: Data was retrospectively collected from medical histories and a total of 39 variables were defined from a literature review. Only adult’s patients referred to polysomnography and with suspicion of obstructive sleep apnea at the Vila Nova de Gaia/Espinho Hospital Center were included. A pre-processing analyse of the data were performed, and continuous variables were categorized. Two datasets were obtained and two plus two Bayesian models were build (Naïve Bayes and Tree augmented Bayesian networks. The sensitivity and specificity were analysed to determine their performance.

Results: We considered for building the models 194 patients, 128 (66%) with obstructive sleep apnea diagnosis. The first dataset have missing values and was used the selection of the significant variables. The second dataset, with the assumption “No” in the missing values, were used to build the two plus two models. This and the dataset from a previous work were comparable and significance differences were found, leading to the use of these new datasets. The chosen model were Tree augmented Bayesian network with the selection variables: gender; neck circumference; craniofacial and upper airway abnormalities; witnessed apneas; nocturia; alcohol before sleep; Epworth Somnolence Scale; concentration decrease; atrial fibrillation; stroke; myocardial infarction; truck driver and daytime sleepiness, with sensitivity of 81% and a positive predictive value of 76%.

Discussion: Our study reveals a proportion of 34% of normal results obtained in polysomnography, leading to the need of a good clinical decision support tool.

Keywords: obstructive sleep apnea, risk factors, diagnosis, Bayesian network, clinical model, sensitivity and specificity
Resumo

Introdução: Na Síndrome da Apneia Obstrutiva do Sono, o esforço respiratório é mantido mas há diminuição/ausência da ventilação devido à oclusão parcial/total da via aérea superior. Afeta 4% dos homens e 2% das mulheres da população mundial. Os principais fatores de risco são a obesidade, idade avançada e gênero masculino. O seu diagnóstico é baseado em sinais e sintomas durante um estudo do sono – polissonografia.

Objetivo: Definir um novo método auxiliar de diagnóstico que suporta a decisão de realizar polissonografia, baseado em sinais e sintomas, priorizando pacientes.

Métodos: Os dados foram recolhidos retrospetivamente, a partir dos diários médicos, e um total de 39 variáveis foram definidas por uma revisão da literatura. Apenas pacientes adultos referenciados para polissonografia e com suspeita da síndrome, encaminhados para o Centro Hospitalar de Vila Nova de Gaia/Espinho, foram incluídos. Efetuou-se uma pré-análise aos dados para categorização das variáveis. Duas bases de dados foram obtidas e duas mais duas redes Bayesians foram construídas (Naive Bayes and Tree augmented Bayesian network). A sensibilidade e especificidade foram analisadas para determinar a validade dos modelos.

Resultados: Na construção das bases de dados foram considerado 194 pacientes, sendo que 128 (66%) apresentavam a síndrome. A primeira base continha informação em falta e foi utilizada na seleção das variáveis significativas. A segunda, com a assunção “Não” na informação em falta, foi usada na construção dos dois mais dois modelos. Esta base e a base de um trabalho prévio foram comparadas. O modelo escolhido foi o Tree augmented Bayesian network com as variáveis selecionadas: gênero; circunferência do pescoço; anormalidades craniomaxilares; apneias presenciadas; álcool antes de dormir; Escala de Sonolência de Epworth; diminuição da concentração; fibrilação auricular; acidente vascular cerebral; enfarte; camionista e sonolência diurna, com uma sensibilidade de 81% e valor positivo preditivo de 76%.

Discussão: O nosso estudo revela uma proporção de 34% de exames normais obtidos com a polissonografia, levando à necessidade de um melhor modelo de suporte à decisão.

Palavras-chave: apneia obstrutiva do sono, fatores de risco, diagnóstico, rede Bayesiana, modelo clínico, sensibilidade e especificidade
Preamble

The interest in this thesis, firstly began with my previous thesis coming to an end. I have a Degree in Physiology, and I have worked in Respiratory Physiology. This was my favourite area in my course. But the circumstances led me to a change. And I don’t regret it.

The sleep area has several mysteries that probably fascinate me but my real interest in this thesis was the use of Bayesian Networks. In the first year of the Master’s degree we had a subject that talks a little bit about this theme, but I was lucky to attend a summer course on Bayesian Networks. This rose my curiosity and interest.

The teacher had a previous student that had studied Obstructive Sleep Apnea and the use of Bayesian Networks, and so, we decided to refresh and upgrade this.

We created a new dataset, although in the same Hospital Center – Vila Nova de Gaia & Espinho. We applied new methods, tried to reach new results and confirm them. Also, we tried to lead this to the primary care.

As everyone knows, the primary care, should be the first way in the Health System, but this is not what is happening. The Hospitals are receiving and treating patients that should be taken care of in the first care. We are talking of obstructive sleep apnea patients.

Their screening should be more accurate. The Sleep Laboratories in the country are not capable of applying tests, like polysomnography, to all the patients. So, we need to find a better way to manage and optimize resources.
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Abbreviations

AASM: American Academy of Sleep Medicine
AC: Abdominal circumference
ACES: Groups of primary care centres
AHI: Apnea-hypopnea index
AUC: Area under the curve
BMI: Body mass index
BN: Bayesian networks
BQ: Berlin questionnaire
CV: Cross-validation
COPD: Chronic Obstructive Pulmonary Disease
CPAP: Continuous Positive Airway Pressure
ESS: Epworth Sleepiness Scale
HC: Hill climbing
NB: Naïve Bayes
NC: Neck circumference
NHS: National Health Service
NPV: Negative predictive value
OSA: Obstructive sleep apnea
PM: Portable monitors
PPV: Positive predictive value
PSG: Polysomnography
ROC: Receiver Operating Characteristic
TAN: Tree augmented Bayesian network
USF: Family Health Unit
WA: Witnessed apneas
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Thesis Organization

Chapter 1 (Introduction) - an introduction to the problem with its definition and context were written not forgetting the relevance of the problem that motivates this thesis.

Chapter 2 (Aim) - our main objective is to define a new auxiliary diagnostic method that can support the decision to perform polysomnography, based on signs and symptoms, prioritizing patients.

Chapter 3 (Background) – key concepts like sleep apnea, risk factors, diagnosis, treatment and Bayesian network are explained. This definitions try to help the thesis perception.

Chapter 4 (Methods) – all the methodology used to develop this thesis are place here. Data collection, variables, models and a flow diagram are present.

Chapter 5 (Results) – detail results are written, with table and figures illustrate it.

Chapter 6 (Discussion) – the risk and diagnostics factors for obstructive sleep apnea achieved in this thesis are compared with the literature. Also, advantages of the Bayesian network are enumerate.

Chapter 7 (Conclusion) – a brief text of our results and their explanations are expose. Also, an end message is present.

Chapter 8 (Future work) – the thinking next of our results and the new risk factor.
Scientific results

1. Introduction
1. Introduction

Sleep apnea has been recognised throughout human history, dating as far back as the 4th century BC. Numerous reports throughout the 19th century and the early part of the 20th century AD gave way to systematically conducted studies on patients with obstructive sleep apnea (OSA) and related syndromes (Jennum & Riha, 2009).

Apnea is defined as the complete cessation of airflow for at least 10 seconds and a hypopnea is defined as a reduction in airflow (30-50%) that is followed by an arousal from sleep or a decrease in oxyhaemoglobin saturation (3-4%) (Chung, Jairam, Hussain, & Shapiro, 2002; Jamie C M Lam, Sharma, & Lam, 2010). There are three types of apneas: central, mixed and obstructive. Central sleep apnea is defined as reduced respiratory effort resulting in reduced or absent ventilation. Mixed apnea is often characterized by starting with central apneas and ending with obstructive events (Brostrom et al., 2012; Jamie C M Lam et al., 2010). In OSA, respiratory effort is maintained but ventilation decreases or disappears because of partial or total occlusion in the upper airway (Chung et al., 2002; Jamie C M Lam et al., 2010; Lee, Won; Nagubadi, Swamy; Kryger, Meir; Mokhlesi, 2008; Mansfield, Antic, & McEvoy, 2013; Robichaud-Hallé, Beaudry, & Fortin, 2012).

OSA was first properly documented in neurophysiological sleep laboratories using techniques developed for the investigation of other conditions such as depression and narcolepsy. It was first described as such in 1965 and there has been an explosion in the facilities for its diagnosis and treatment as well as rapid advancement in the understanding of its far-reaching consequences (Jennum & Riha, 2009). OSA severity is assessed with apnea-hypopnea index (AHI), which is the number of apneas and hypopneas per hour of sleep (Jamie C M Lam et al., 2010). According to the American Academy of Sleep Medicine (AASM) recommendations, OSA is defined with AHI≥5, and it is classified as mild OSA with AHI of 5 to 15; moderate OSA with AHI of 16 to 30; and severe OSA with AHI ≥30 (Chung et al., 2002; Corral-Peñafile, Pepin, & Barbe, 2013; Epstein et al., 2009; Jamie C M Lam et al., 2010).

Approximately 30% of the general public are affected by a significant sleep problem, often of long standing, with much higher rates in certain groups such as the elderly, those with a psychiatric disorder or learning disability, and others who have neurological or other medical disorders (Stores, 2007). OSA affects about 4% of men and at least 2% of
women (Brostrom et al., 2012; Corral-Peñaﬁel et al., 2013; Epstein et al., 2009; Jennum & Riha, 2009; Stores, 2007).

The signs, symptoms and consequences of OSA are a direct result of the derangements that occur due to repetitive collapse of the upper airway: sleep fragmentation, hypoxemia, hypercapnia, marked swings in intrathoracic pressure, and increased sympathetic activity. Clinically, OSA is defined by the occurrence of daytime sleepiness, loud snoring, changes in personality and adverse effects on social life and performance at work, as well as intellectual deterioration to the extent that dementia is suspected, witnessed breathing interruptions, or awakenings due to gasping or choking (Corral-Peñaﬁel et al., 2013; Epstein et al., 2009; Stores, 2007).

Risk factors for developing OSA include obesity (body mass index (BMI) ≥30), snoring, aging, increased neck circumference (NC) and increased abdominal circumference (AC), hypertension, pulmonary hypertension, congestive heart disease, atrial ﬁbrillation, coronary artery disease, ﬁrst-ever stroke, gastroesophageal reﬂux, primary open-angle glaucoma, heart transplants, hypothyroidism, diabetes, anxiety, heavy alcohol consumption, history of smoking, male sex, postmenopausal status, high-risk driving populations (such as truck drivers), those being evaluated for bariatric surgery, and family history (Chung et al., 2002; Corral-Peñaﬁel et al., 2013; Epstein et al., 2009; Jamie C M Lam et al., 2010; Lee, Won; Nagubadi, Swamy; Kryger, Meir; Mokhlesi, 2008).

Diagnostic criteria for OSA are based on clinical signs and symptoms determined during a comprehensive sleep evaluation, which includes a sleep oriented history and physical examination, and ﬁndings identiﬁed by sleep testing (Epstein et al., 2009; Mansﬁeld et al., 2013). A comprehensive sleep history in patients suspected of OSA should include an evaluation for snoring, witnessed apneas (WA), gasping/chocking episodes, excessive daytime sleepiness not explained by other factors, including assessment of sleepiness severity by the Epworth Sleepiness Scale (ESS), non-refreshing sleep, total sleep amount, nocturia, morning headaches, sleep fragmentation/sleep maintenance insomnia, decreased libido, irritability and decreased concentration and memory (Epstein et al., 2009; Jamie C M Lam et al., 2010). The presence of at least 5 obstructive respiratory events (apneas, hypopneas or respiratory effort related arousals) per hour of sleep or the presence of 15 or more obstructive respiratory events per hour of sleep in the absence of sleep related symptoms is also sufﬁcient for the diagnosis of OSA (Epstein et al., 2009; Stores, 2007). The diagnosis must be established by an acceptable method being the two accepted methods of objective testing the in-laboratory polysomnography (PSG) and home testing with portable monitors (PM) (Blondet et al., 2009; Chung et al., 2002; Corral-Peñaﬁel et al., 2013; Epstein et al., 2009; Jennum & Riha, 2009; Jamie C M Lam et al., 2010; Stores, 2007). PSG is time consuming, labour intensive, limited to urban areas, and costly (Jennum & Riha, 2009; Jamie C M Lam et al., 2010). PM tends to underestimate the severity of OSA, because it doesn’t allow determination of sleep efficiency (Jennum & Riha, 2009).
Despite the recent advances in diagnostic technology in the field of sleep medicine and increased awareness of OSA by the public, a majority of those affected are still undiagnosed, making sleep apnea vastly under recognized in primary practice (Chung et al., 2002; Jennum & Riha, 2009). Researchers estimate that 82% of men and 93% of women with moderate-to-severe OSA have not been clinically detected or diagnosed. It is important to emphasize that primary physicians should assess their patients’ medical status thoroughly before referring them for a sleep study (Chung et al., 2002). Busy primary care physicians are routinely challenged by the need to add information about medical conditions to their store of knowledge. The substantial medical, social, and economic consequences of untreated OSA; the overwhelming number of patients who have escaped clinical detection; and the likelihood of successful treatment strongly justify screening for this disease. Routinely asking patients about loud snoring, excessive daytime sleepiness, and unsatisfactory sleep will better serve primary care patients and advance diagnosis and treatment of OSA (Chung et al., 2002).

OSA is considered to be a long-standing illness and the associated complications seem to impose an economic burden in our society, affecting both developing and developed countries all over the world (Jamie C M Lam et al., 2010). This significant socioeconomic burden relays in comorbidity, healthcare utilization in the primary and secondary healthcare sectors, use of medication, effects on employment and lost income. Therefore, it is important for primary care physicians and specialists to be competent to recognise and identify those affected subjects for early and appropriated treatments (Jennum & Riha, 2009).

Nowadays, prediction models are generated by artificial intelligence, using decision trees, neural networks, support vector machines and Bayesian networks (BN). All of this should have good performance, good ability to handle data entry errors or omissions, transparency of diagnostic knowledge, ability to explain decisions, and the algorithm should be able to reduce the number of tests needed for making a reliable diagnosis. Its tools have been used in sleep medicine to create models alternative of those based in logistic regression. BN have been used in medical domain in some areas with high performance like pneumonia and breast cancer (Leite, 2012).

Previous thesis “Refining pre-polysomnography suspicion of Obstructive Sleep Apnea Syndrome: Logistic and Bayesian analysis of clinical factors” written by MD Liliana Leite, affirms that in Portugal, patients referred by the primary care physician to a sleep consult, based on clinical factors, have a specificity of the entire process of 48% of PSG performed in 2010, in Vila Nova de Gaia/Espinho Hospital Center, with a negative result for OSA, from which 75% had a completely normal result. It’s also said that prediction models, consisting in simple decision rules, prognostic score and classification of patients into different risk categories, have a main limitation: sensitivity.
These models need a high sensitivity, as false negatives should be avoided, to prevent excluding patients with moderate or severe OSA from performing PSG. Another problem in the application of these models is the lack of internal and/or external validation of the results (Leite, 2012). This work studied several factors and identified six as associated with OSA diagnosis (BMI, NC and AC, gender, WA and alcohol consumption before sleep) but this made the results not generalizable to use in primary care. Also, the BN were developed based only on variables univariately associated with the outcome, yielding a bias on the possible knowledge representation of the models. This is why emerge the need to revisit the OSA cohort, develop and validate a new Bayesian network-based decision support system that can be used in the future. In this we use all 33 variables, creating a model with a high interpretability, high discriminated power and better accuracy, sensitivity and precision cross-validation (CV). But more studies are needed to better fit this clinical decision support model tool and also the need to integrate a much wider set of clinical variable (Rodrigues, Pedro Pereira; Santos, Daniela Ferreira; Leite, 2015).
2. Aim
2. Aim

The proposal is to define a new auxiliary diagnostic method that can support the decision to perform polysomnography, based on clinical data.

The secondary objectives are to:

- Reduce the number of unnecessary PSG;
- Avoid false negatives;
- Prioritize patients recommended for PSG or PM;
- Expand the Bayesian network results, and
- Produce an evaluation protocol model for use in the primary setting.
3. Background
3. Background

The human upper airway is a unique multipurpose structure involved in performing functional tasks such as speech, swallowing of liquids/food, and the passage of air for breathing. The airway is composed of numerous muscles and soft tissues but lack rigid or bony support (Eckert & Malhotra, 2008). The upper airway includes the pharynx and the nasal cavities. The pharynx can be divided into the nasopharynx, laryngopharynx and oropharynx, being the only collapsible segment of the respiratory tract. The nose is composed of bone and cartilage attached to the facial skeleton. It is a pyramidal structure that is divided by a midline septum into two nasal cavities. The nasal cavities are lined with mucosa that can function to heat and humidify inspired gas. The posterior portion of the mouth opens into the oropharynx, so when a patient is in supine position or unconscious, the tongue and lower jaw may slide posteriorly leading to airway obstruction (Nemergut & Kopp, 2013).

3.1 Pathophysiology

OSA is characterized by recurrent collapse of the pharyngeal airway during sleep, resulting in substantially reduced (hypopnea) or complete cessation (apnea) of airflow despite ongoing breathing efforts. These disruptions to breathing lead to intermittent blood gas disturbances (hypercapnia and hypoxemia) and surges of sympathetic activation (Eckert & Malhotra, 2008; Romero, Krakow, Haynes, & Ulibarri, 2010).

The pathophysiological causes of OSA likely vary considerably between individuals. Important components likely include upper airway anatomy, the ability of the upper airway dilator muscles to respond to respiratory challenge during sleep, the propensity to wake from increased respiratory drive during sleep (arousal threshold), the stability of the respiratory control system (loop gain), and the potential for state-related changes in lung volume to influence these factors (Chung et al., 2002; Eckert & Malhotra, 2008; Jamie C M Lam et al., 2010).
One mechanism believed to be important in the pathogenesis of OSA relates to the interaction between pharyngeal anatomy and a diminished ability of the upper airway dilator muscles to maintain a patent airway during sleep. During wakefulness, patients with OSA appear to compensate for an anatomically compromised upper airway through protective reflexes which increase upper airway dilator muscle activity to maintain airway patency (Chung et al., 2002; Eckert & Malhotra, 2008).

Ventilatory control stability is believed to be an important contributor to OSA pathogenesis because it creates a cyclical breathing pattern that develops, whereby the patient oscillates between obstructive breathing events (sleep) and arousal (wakefulness). Ventilatory control stability can be described using the engineering concept loop gain. Essentially, loop gain is a term used to describe the stability of a system controlled by feedback loops. In the context of ventilatory control, loop gain refers to the stability of the respiratory system and how responsive the system is to a perturbation to breathing (arousal). In other words, loop gain can be considered as the propensity for the ventilatory control system to develop cyclical fluctuations in ventilatory output (Eckert & Malhotra, 2008).

The interaction between pharyngeal patency and lung volume is believed to be an important contributor to OSA pathogenesis. Indeed, upper airway mechanics can be modulated by changes in lung volume during wakefulness and sleep in healthy individuals (Eckert & Malhotra, 2008).

OSA has long been recognized as a heterogeneous disorder with potentially multiple contributing pathophysiological causes, the relative contributions of which may vary considerably between patients (Eckert & Malhotra, 2008).

### 3.2 Severity levels

The severity of OSA has two components: the severity of daytime sleepiness and of overnight monitoring. The severity should be specified for both components and the rating severity should be based on the most severe component (“Practice parameters for the use of portable recording in the assessment of obstructive sleep apnea. Standards of Practice Committee of the American Sleep Disorders Association,” 1994).

- **Daytime sleepiness**
  a. Mild: unwanted sleepiness or involuntary sleep episodes occur during activities that require little attention. Symptoms produce minor impairment of social or occupational function.
  b. Moderate: unwanted sleepiness or involuntary sleep episodes occur during activities that require some attention. Symptoms produce moderate impairment of social and occupational function.
c. Severe: unwanted sleepiness or involuntary sleep episodes occur during activities that require more active attention. Symptoms produce marked impairment in social or occupational function.

- Overnight monitoring (AHI):
  a. Mild: 5 to 15 events per hour.
  b. Moderate: 15 to 30 events per hour.
  c. Severe: greater than 30 events per hour.

### 3.3 Risk factors

The major risk factors for OSA include advanced age, male sex and obesity, although the underlying mechanisms remain unclear (Al Lawati, Patel, & Ayas; Davies, Ali, & Stradling, 1992; Doghramji, 2008; Hoffstein & Szalai, 1993; Kapur, 2010; Kohler, 2009; Jamie C M Lam et al., 2010; Manber & Armitage, 1999; Pagel, James; Hirshkowitz, Max; Doghramji, Paul; Ballard, 2008; Romero et al., 2010; Wall, Smith, & Hubbard, 2012; Terry Young, Evans, Finn, & Palta, 1997; Terry Young et al., 2002; Terry Young, Skatrud, & Peppard, 2004).

Common symptoms of patients with OSA are (Chung et al., 2002; Jennum & Riha, 2009; Jamie C M Lam et al., 2010; Mattei, Tabbia, & Baldi, 2004; Stores, 2007):

- Excessive daytime sleepiness;
- Loud snoring, stopped or shallow breathing or chocking during sleep;
- Unrefreshing sleep, possible with nocturia;
- Weight gain or more body fat in neck or chest or abdomen;
- Irritability, mood changes, and loss of libido, can mimic depression/anxiety.

Less common features of OSA (Chung et al., 2002; Jennum & Riha, 2009; Jamie C M Lam et al., 2010; Mattei et al., 2004; Romero et al., 2010; Stores, 2007):

- Nocturnal manifestations:
  - Gasping for air; Shortness of breath;
  - Chronic mouth breathing;
  - Frequent awakenings;
  - Restless sleep;
  - Gastroesophageal reflux;
  - Nocturnal panic attacks;
  - Excessive sweating;
  - Nocturnal cyclical bradycardia;
  - Nocturia.
• Daytime manifestations:
  o Lack of energy, tiredness, fatigue (increases risk for automobile accidents);
  o Daytime naps are not refreshing;
  o Morning headaches;
  o Feeling of morning “drunkenness”;
  o Bilateral leg edema.

There are some features that need to be evaluated that may suggest the presence of OSA: increased NC (>42 cm in men, >37 cm in women), increased AC (>94 cm in men, >80 cm in women), a Modified Mallampati score of 3 or 4, the presence of retrognathia, lateral peritonsillar narrowing, macroglossia, tonsillar hypertrophy, elongated/enlarged uvula, high arched/narrow hard palate, nasal abnormalities (polyps, deviation, valve abnormalities, turbinate hypertrophy) and/or overjet (Epstein et al., 2009; Mattei et al., 2004; Romero et al., 2010).

3.3.1 Age

OSA occurs throughout the entire lifespan, from neonates to the elderly. In adults, the frequency of disordered breathing during sleep increases with age and is poorly associated with an increased incidence of daytime sleepiness or other symptoms of OSA (Jennum & Riha, 2009; Lee, Won; Nagubadi, Swamy; Kryger, Meir; Mokhlesi, 2008). Mean age of death among people with untreated OSA is 59 years (Chung et al., 2002).

With the advancing age, sleep quality decreases and sleep-related difficulties are more common (Madani & Madani, 2009). Possible explanations are changes in upper-airway calibre, attenuation in the ventilatory response to hypoxia and hypercapnia, decreases in functional activity of the upper airway, and an increase in the variability of ventilation during sleep. One of the mechanisms proposed for the increased prevalence of sleep apnea in the elderly include increased deposition of fat in the pharyngeal area, lengthening of the soft palate (Jamie C M Lam et al., 2010).

3.3.2 Gender

For an overall estimation across different countries, it is approximately 3-7 per cent for adult men and 2-5 per cent for adult women in the general population. Thus, OSA is more common in men, approximately 2 to 3 times that of women (Jennum & Riha, 2009; Jamie C M Lam et al., 2010).

It is not clear why OSA is more common in men than in women. It can be attributed to anatomical and functional properties of the upper airway and in the ventilator response to the arousals from sleep, the clinical presentation, different tolerance of symptoms, differing amount of medical services, or bias by physicians expecting a higher male predominance. Besides, hormonal differences may play a role in the predisposition to abnormal breathing during sleep. Pre-menopausal women are relatively protected from
OSA even if they have other known risk factors for OSA (Dursunoglu, Ozkurt, & Sarikaya, 2009; Jennum & Riha, 2009; Jamie C M Lam et al., 2010; Lee, Won; Nagubadi, Swamy; Kryger, Meir; Mokhlesi, 2008; Resta et al., 2005).

Also, the way that men and women perceive and relate symptoms of sleep are reported differently (Dursunoglu et al., 2009; Madani & Madani, 2009; Resta et al., 2005). Women are less unlikely to report classic symptoms like snoring, gasping or choking, WA. They pay more attention to report fatigue and lack of energy (Dursunoglu et al., 2009; Madani & Madani, 2009).

### 3.3.3 Obesity

OSA is a prevalent and severe condition in close association with obesity (BMI) epidemic globally (Chung et al., 2002; Jamie C M Lam et al., 2010; Lee, Won; Nagubadi, Swamy; Kryger, Meir; Mokhlesi, 2008; Wall et al., 2012). Obesity or visceral obesity is thought to be associated with anatomic alterations that predispose to upper airway obstruction during sleep, by increasing adiposity around the pharynx and body. In subjects with severe obesity, BMI>40, the prevalence of sleep apnea was markedly increased to 40-90 per cent. It is well demonstrated that a 10 per cent body weight reduction was associated with a parallel 26 per cent decrement in AHI (Jamie C M Lam et al., 2010).

### 3.3.4 Excessive daytime sleepiness

The main symptom of untreated OSA is hypsomnolence or excessive daytime sleepiness that often manifests as dozing off in meetings or while reading, watching television, or driving (greatest impact from the public health perspective) (Chung et al., 2002; Jennum & Riha, 2009). Some patients, especially women, describe a lack of energy and tiredness or fatigue rather than sleepiness (Chung et al., 2002).

Sleepiness can be regarded as “normal” sleepiness (a result of the normal circadian rhythm) and “pathological” sleepiness (a result of altered sleep scheduling). Pathological sleepiness can be subdivided into “habitual” (OSA) or “occasional” (jet lag) (Jennum & Riha, 2009).

To evaluate daytime sleepiness the widest questionnaire is ESS, first devised in 1991. It consists of eight items and the patient is asked to score (on a 0 to 3 scale) how likely he/she is to doze off. The maximal score is 24 and normal subjects score between 0 and 10. Scores greater than 10 are usually considered an indication of daytime sleepiness (Jennum & Riha, 2009; Johns, 1991). This measures propensity for daytime sleep in adults with an internal consistency (Cronbach’s α) of 0.88, and at a cut off score of >10. This measure has a 94% sensitivity and 100% specificity. Its advantages include ease of administration and low cost and it is independent of short-term variations in sleepiness with no time relation of day and also of inter-day variations. While this questionnaire is
not specifically diagnostic for OSA, it is a useful indicator of general sleep disorders (Chung et al., 2002; Di Guardo et al., 2010; Jennum & Riha, 2009; Johns, 1991).

3.3.5 Snoring and Nocturia

Snoring is a common complaint, but by itself does not definitely imply presence of OSA (Chung et al., 2002; Wall et al., 2012). Reports published in the 1990s suggested a relationship between self-reported snoring and familial occurrence of snoring and sleep apnea, with a relative risk association of 3-5. The risk has been demonstrated to increase if both parents are affected (Jennum & Riha, 2009). It results from vibration and turbulence in the airways and its degree of blockage across airway segments determines the quality and intensity of snoring (Mattei et al., 2004).

Nocturia is the condition of getting up to urinate once or multiple times during the night. This is the most common and well-researched symptom of OSA and is related to increased negative intrathoracic pressure swings due to sleep breathing events. Despite this mechanism, primary care physicians are not encouraged to use nocturia when assessing OSA risk. In fact, nocturia is not recognized as an OSA symptom in the AASM (Romero et al., 2010).

3.3.6 Neck and abdominal circumference

NC and AC is also described as a risk factor for OSA. This is related to obesity, because of the previous referred anatomic alterations that lead to upper airway collapse during sleep. The excess of adipose tissue in the area of the neck and belly will compress the respiratory tract. A neck size bigger than 37 cm in women and 42 cm in men, and an abdominal size bigger than 94 cm in men and 80 cm in women are considered clinically significant (Davies et al., 1992; Doghramji, 2008).

3.3.7 Craniofacial and upper-airway structure

Previous studies have shown that craniofacial abnormalities are important in the pathogenesis of OSA, particularly in non-obese patients. Differences in craniofacial morphology may explain some of the variation in risk of OSA in different ethnic groups (Jamie C M Lam et al., 2010).

The structural factors in the upper airway may alter its mechanical properties. Abnormal characteristics can alter this mechanical properties and increase its propensity to collapse during sleep, such as enlarged tonsils, enlarged uvula, “narrow airway”, macroGLOSSIA, retroplaced mandible, soft tissue, tonsillar hypertrophy, inferiorly positioned hyoid bone, and decreased posterior airway space (Doghramji, 2008; Jamie C M Lam et al., 2010; Madani & Madani, 2009; Punjabi, 2008; Yaggi & Strohl, 2010; Terry Young et al., 2004).
3.3.8 Ethnicity

The prevalence of OSA appears to vary among ethnic groups. The discrepancy in prevalence is most likely associated with a propensity of known risk factors for OSA in certain cultural groups, although anthropometrical variables and genetic predisposition could also play a role (Blondet et al., 2009; Lee, Won; Nagubadi, Swamy; Kryger, Meir; Mokhlesi, 2008). Chinese patients tend to be younger and have a lower BMI than white patients, but they present more severe underlying craniomandibular abnormalities (Chung et al., 2002). Inter-ethnic studies suggest that African-American ethnicity may also be a significant risk factor for OSA (Jamie C M Lam et al., 2010).

3.3.9 Genetics/Family history

Familial aggregation and genetic factors are thought to play a role in the development of OSA. First degree relatives of those with OSA increases the relative risk compared to those without OSA by 1.5-2.0, and familial susceptibility to OSA increases directly with the number of affected relatives. Obesity is closely associated with OSA and itself aggregates in families, so it is possible that familial aggregation of OSA is related to the genetics of obesity (Jamie C M Lam et al., 2010).

3.3.10 Smoking, alcohol and sedatives

Cigarette smoking and alcohol have been shown to be risk factors for OSA. Smoking is associated with a higher prevalence of snoring and sleep-disordered breathing. It can be explained by the cigarette-induced airway inflammation and damage which could change the structural and functional properties of the upper airway, and increasing the risk of collapsibility during sleep. Alcohol relaxes upper airway dilator muscles, increases upper airway resistance and may induce OSA in susceptible subjects. Therefore, alcohol intake can prolong apnea duration, suppress arousals, increase frequency of occlusive episodes and worsen the severity of hypoxaemia, even though the underlying mechanisms are not well understood (Jennun & Riha, 2009; Jamie C M Lam et al., 2010).

3.3.11 Comorbid conditions

World population is at risk of co-occurrence of two or more chronic diseases – multimorbidity. Nine out of ten primary care patients had more than one chronic condition, while approximately 50% had five or more. Multimorbidity has been associated with several adverse effects, such as a reduction in the quality of life, increase in physiological distress, medical complications and increased mortality. (Robichaud-Hallé et al., 2012)

Sleep disturbance can exacerbate pre-existing medical and psychiatric disorders (Alam, Chengappa, & Ghinassi, 2012; Epstein et al., 2009). OSA appears to occur more frequently in people with psychiatric disorders than with other medical conditions, being more common in patients with schizophrenia (Alam et al., 2012).
OSA can worsen epilepsy, systemic hypertension and cardiac failure, but it can also be implicated (possible concomitant problems) in pulmonary hypertension, stroke, myocardial infarction, cor pulmonale, decreased daytime alertness, motor vehicle accidents, cardiovascular and cerebrovascular disease, diabetes mellitus, arrhythmia, coagulability, endothelial dysfunction and inflammation (Epstein et al., 2009; Jennum & Riha, 2009; Jamie C M Lam et al., 2010; Robichaud-Hallé et al., 2012; Stores, 2007).

There is increasing evidence that OSA is an independent risk factor for an adverse cardiometabolic profile, although much of the causal role and mechanisms are still poorly understood (Dursunoglu et al., 2009; Jamie C M Lam et al., 2010). Despite the lack of controlled studies, several studies have presented data showing that weight reduction through dieting or bariatric surgery is followed by a reduction in AHI and incidence of diabetes, improved glucose control and reductions in hyper-triglyceridaemia (Jennum & Riha, 2009). Type 2 diabetes mellitus and OSA share a number of common risk factors, including advancing age, ethnicity and obesity. Diabetes is a major cause of morbidity and mortality linked to microvascular and macrovascular complications and is considered as a coronary artery disease risk equivalent for myocardial infarction (Cass, Alvah; Alonso, Jerome; Islam, Jamal; Weller, 2013).

The morbidity and association between hypertension and untreated OSA is well established and is independent of confounding factors (age, sex, BMI) but is still unclear: untreated OSA might trigger slight elevations (5 to 10 mmHg) in diastolic and nocturnal systolic blood pressure (Chung et al., 2002; Di Guardo et al., 2010). A proposed mechanism is the sympathetic activation and increased levels of catecholamine’s causing inflammation, arterial stiffness and atherosclerosis, due to apnea-related oxygen desaturations. Another one is the shared risk of obesity (Brostrom et al., 2012; Broström et al., 2012; Pagel, James; Hirshkowitz, Max; Doghramji, Paul; Ballard, 2008). Nevertheless, in patients with untreated OSA, clinically significant systemic or pulmonary hypertension can develop over time, especially when OSA is severe and patients have a greater number of risk factors for hypertension. Physicians should be aware that hypertension associated with untreated OSA is often intractable, and that a high prevalence (56%) of OSA has been observed in men with therapy-resistant hypertension (Brostrom et al., 2012; Chung et al., 2002)

Patients with OSA and moderate-to-severe coexisting lung disease, such as Chronic Obstructive Pulmonary Disease (COPD), are more likely to develop type II respiratory failure that will improve with treatment of obstructive apneas. Likewise, nocturnal asthma may be worsened by sleep apnea and treatment may lead to improvement (Greenberg-Dotan et al., 2014; Jennum & Riha, 2009).

OSA leads to neuropsychological impairment that includes deficits in attention, concentration, vigilance, manual dexterity, visuomotor skills, memory, verbal fluency and executive function (Jennum & Riha, 2009).
The pathophysiological interaction between OSA and cardiovascular disease is complex and comprises sympathetic activation, inflammation, oxidative stress and endothelial dysfunction (Pagel, James; Hirshkowitz, Max; Doghramji, Paul; Ballard, 2008; Wachter et al., 2013).

The social and cardiovascular consequences of OSA seem most pronounced among patients of low socioeconomic status. It should be noted, however, that there is a tendency towards lower screening and diagnostic activity among people of lower social status (Jennum & Riha, 2009).

### 3.4 Diagnosis

The consequences of undiagnosed and untreated OSA are not trivial because the quality of life for patients is seriously impaired (Chung et al., 2002). As part of the initial sleep evaluation, and prior to objective testing, patients should receive education regarding possible diagnoses, diagnostic steps, and the procedure involved in any testing (Epstein et al., 2009).

A screening questionnaire for use with adult patients can be a useful starting point in assessment (Mansfield et al., 2013; Stores, 2007). A structured sleep diary, recording day and night events over 1-2 weeks, may also reveal further valuable information. Other potentially relevant details may be contained in the patient’s medical, psychiatric and social histories, including occupational factors and also habits (such as caffeine, alcohol or nicotine consumption and use of illicit drugs) which might affect sleep. These enquiries should be accompanied by a review of systems, as well as physical and mental state examination. It is important to identify any neurological, general medical or psychiatric disorder likely to affect sleep, or physical anomalies. A family history of sleep disorder might also be revealing (Stores, 2007).

The diagnosis of OSA is confirmed if the number of obstructive events (apneas, hypopneas + respiratory event related arousals) on PSG is greater than 15 events/hour or greater than 5/hour in a patient who reports any of the following: unintentional sleep episodes during wakefulness; daytime sleepiness; waking up breath holding, gasping or choking; or the bed partner describing loud snoring, breathing interruptions, or both during the patient’s sleep (Epstein et al., 2009).

In view of the high prevalence of OSA and the difficulty in its diagnosis, better tools are needed to adequately screen susceptible populations and help decide who should be tested (Blondet et al., 2009).
3.5 Polysomnography

High-risk patients with nocturnal symptoms of OSA should undergo sleep testing, including those who are obese, those with systolic or diastolic heart failure, coronary artery disease, history of stroke or transient ischemic attacks, or significant tachyarrhythmias or bradyarrhythmias. Patients with congestive heart failure who continue to have nocturnal symptoms of sleep related breathing disorders despite optimal medical management are also at risk for OSA and should undergo testing. Patients with hypertension should undergo evaluation and testing if they have nocturnal symptoms (disturbed sleep, nocturnal dyspnea, or snoring) suggestive of OSA or if they remain hypertensive despite optimal medical management (Epstein et al., 2009).

The gold standard diagnostic test for OSA is the overnight in-laboratory polysomnography. It involves multi-channel continuous polygraphic recording from surface leads for electroencephalography, electro-oculography, electromyography, electrocardiography, nasal pressure transducer (supplemented by thermistor) for nasal airflow, thoracic and abdominal impedance belts for respiratory effort, pulse oximetry, tracheal microphone for snoring, and sensors for leg and sleep position. These recordings will identify different types of apneas and hypopneas during sleep (Blondet et al., 2009; Chung et al., 2002; Epstein et al., 2009; Jennum & Riha, 2009; Jamie C M Lam et al., 2010; Redeker, 2005). This requires an overnight stay in the hospital with trained staff who are capable of monitoring and interpreting the real-time complicated physiologic data throughout the night (Epstein et al., 2009; Jamie C M Lam et al., 2010).

This test and its interpretation is technically time-consuming, expensive and intakes long waiting lists (Blondet et al., 2009; Jennum & Riha, 2009).

3.6 Portable monitors

PM for the diagnosis of OSA should be performed only in conjunction with a comprehensive sleep evaluation. It should, at a minimum, record airflow respiratory effort, and blood oxygenation, include an oronasal thermal sensor to detect apneas, a nasal pressure transducer to measure hypopneas, oximetry, and ideally, calibrated or uncalibrated inductance plethysmography for respiratory effort. An experienced sleep technician, sleep technologist, or appropriately trained healthcare practitioner must perform the application of PM sensors or directly educate the patient in the correct application of the sensors. PMs may be used in the unattended setting as an alternative to PSG for the diagnosis of OSA in patients with a high pretest probability of moderate to severe OSA and no comorbid sleep disorder or major comorbid medical disorders when all of the previous parameters are met. The diagnosis of OSA is confirmed and severity determined using the same criteria as used for PSG (Corral-Peñafiel et al., 2013; Epstein et al., 2009).
The term AHI has been defined differently when used with PMs than when used with PSG. AHI PM is the number of apneas + hypopneas / total recording time rather than total sleep time. As a result, PMs are likely to underestimate the severity of events compared to the AHI by PSG (Epstein et al., 2009).

### 3.7 Treatment

The patient should be an active participant in the decision on treatment type and taught to contribute to the management of his or her own disease. The physician should review the results of objective testing with the patient, including education on the nature of the disorder and treatment options. The educational programs should include discussion of the pathophysiology, risk factors, natural history, and clinical consequences of OSA. Treatment options should be discussed in the context of the severity of the patient’s OSA, their risk factors, any associated conditions, and the patient’s expectations (Epstein et al., 2009).

Treatment of OSA causes reduced morbidity, mortality and hospitalisation rates and this has been demonstrated to be cost effective (Jennum & Riha, 2009). Options for OSA patients include modification of body position during sleep, weight loss, continuous positive airway pressure (CPAP), oxygen supplementation, oral appliances, and surgery (Chung et al., 2002; Culpepper & Roth, 2009; Mansfield et al., 2013; Pagel, James; Hirshkowitz, Max; Doghramji, Paul; Ballard, 2008).

Adjunctive management of OSA should include moderating alcohol consumption and avoiding sedatives-hypnotics and narcotics because these are respiratory depressants and might worsen breathing disorders (Chung et al., 2002).

CPAP has been shown unequivocally to alleviate excessive daytime sleepiness; restore quality of life; improve vigilance, concentration, fatigue, and memory; reduce use of health care services, and decrease traffic accidents. CPAP treatment lowers blood pressure, improves cardiac function, and decreases mortality (Chung et al., 2002; Corral-Peñafiel et al., 2013; Epstein et al., 2009).

For patients with comorbid primary depression and OSA, recommendations are to treat the sleep apnea to facilitate managing the depression (Chung et al., 2002; Culpepper & Roth, 2009).

### 3.8 Primary care

For most physicians, the symptoms give a good indication of whether to refer patients for further investigation but this depends on their ability to recognize the disorder and make the appropriate referral, because it is not feasible to send every patient who snores for evaluation. Primary physicians should conduct careful interviews, physical
examinations, and screening for other medical disorders (Broström et al., 2012; Chung et al., 2002; Culpepper & Roth, 2009; Epstein et al., 2009; Mansfield et al., 2013; Stores, 2007).

The physical examination can suggest increased risk and should include the respiratory, cardiovascular, and neurologic systems. Particular attention should be paid to the presence of obesity, signs of upper airway narrowing, or the presence of other disorders that can contribute to the development of OSA or to the consequences of OSA. Routinely asking patients about loud snoring, staying asleep, excessive daytime sleepiness, and unsatisfactory sleep will better serve primary care patients and advance diagnosis and treatment of OSA. Also, the patient’s bed partner or other relative should also be questioned (Broström et al., 2012; Chung et al., 2002; Epstein et al., 2009; Mansfield et al., 2013; Pagel, James; Hirshkowitz, Max; Doghramji, Paul; Ballard, 2008; Stores, 2007).

The following laboratory investigations could be specifically helpful in assessment, diagnosis, and management of OSA and its complications (Broström et al., 2012):

- Complete blood count;
- Electrocardiogram;
- Electrolytes;
- Blood glucose.

Two questionnaires are available and are specifically designed to assist primary care physicians: Berlin Questionnaire (BQ) and ESS. The BQ takes about 5 minutes to complete, it has ten items divided in three categories according to the symptoms: snoring or increased upper resistance, somnolence or chronic fatigue, and presence of hypertension or obesity. This questionnaire is designed for patients with clinically significant OSA (AHI>15), and its positive predictive value (PPV) is 0.97, the specificity 0.97, and the sensitivity 0.54. Apart from these two, no other questionnaires are specific and exclusive for OSA (Ahmadi, Chung, Gibbs, & Shapiro, 2008; Bouloukaki et al., 2013; Chung et al., 2002; Kang et al., 2013; Mattei et al., 2004).

A survey of United Kingdom medical schools revealed that out of a typical 5 year undergraduate course, the median time spent on formal teaching about sleep and its disorders was 5 minutes, therefore, medical staff do not usually enquire about sleep symptoms (Stores, 2007). The annual Sleep in America survey reported that 86% of respondents’ generalists had never discussed sleep with patients. Six of ten healthcare professionals reported not having enough time to discuss sleep problems during office visits. Another study reported that 90% of generalists rated their knowledge of sleep disorders as fair or poor (Hayes, Murray, Castriotta, Landrigan, & Malhotra, 2012).

Portugal chose to protect constitutionally access to health and include in the study design of its health system creating (1979) a National Health Service (NHS), universal, general and also trend free. This was the response that the community found to provide
comprehensively access to health care, depending on need and not their ability to pay, assuming collective responsibility through taxation. As a result of the created device, Portugal has a network of primary care, a hospital network and a more recent continuum of care network. The greatest challenge of our time is the future sustainability of our NHS. Nowadays, it corresponds to a share of 66% of the overall costs that the Portuguese spends on health which tends to double every 10 years, largely due to pressure that therapeutic and technological innovation and the lifetime of the extension have on health systems. After all, the cost to the society by the NHS funding highlights as one of the best investments made by the Portuguese democracy (Ribeiro, 2003).

Primary care centres are responsible for delivering primary health care. They do not have financial or administrative autonomy. It is the Ministry of Health that allocates funds to the regional health administration, which in turn fund the global activity of each health centre through the recently created groups of primary care centres (ACES). In 2006, a reform approved by the government, introduced new models – the Family health unit (USF), which are multidisciplinary teams, paid partially through incentive mechanisms (Barros, Pedro Pita; Machado, Sara Ribeirnho; Simões, 2011).

The objective of these USFs is to promote health and disease prevention, including management of acute or serious health problems according to physical, psychological, social and cultural dimension, through a person-centred approach oriented towards the individual, her/his family and the community of which she/he is member. The services provided by the general physicians are: general medical care for the adult population; prenatal care; children’s care; family planning and perinatal care; first aid; certification of incapacity to work; home visits; preventive service, including immunization. They work with a system of patient’s lists, average 1500 patients, but there are patient’s lists exceeding 2000 patients (Barros, Pedro Pita; Machado, Sara Ribeirnho; Simões, 2011).

The major problems currently faced in primary care include (Barros, Pedro Pita; Machado, Sara Ribeirnho; Simões, 2011):

- An inequitable distribution of health care resources;
- Difficult access to primary health care resulting in emergency department overuse;
- Very limited public provision of services in continuing and home care;
- Mixed options about the public primary health care system;
- Scarcity of quality control programmes;
- A lack of motivation of physicians working in isolation for fixed salaries;
- Limited access to health care services for poorer and geographically isolated people, and
- A shortage of qualified ancillary staff in primary care centres.
3.9 Clinical decision support systems

Nowadays, new computational techniques are available and are better at detecting patterns hidden in biomedical data, being better in representing and manipulating uncertainties. Clinical decision support systems are today a major topic because it may help the diagnosis, prognosis and treatment. However, the complicated nature of real-world bio and medical data take us beyond traditional biostatistics (P. J. F. Lucas, van der Gaag, & Abu-Hanna, 2004). When biomedical data are represented as dichotomous outcomes, the best choice for statistical modelling is logistic regression. This uses the assumption that predictor variables are related in a linear manner to the log odds of the outcome, being unable to deal with great databases. This made the utilization of new methods extremely necessary (Tu, 1996). We are talking about data mining. Data mining allows data pre-processing and visualization, non-statistical methods and new methods based on probabilities and statistics (P. J. F. Lucas et al., 2004).

Another technique is artificial intelligence, more exactly machine learning. It can be described as the study of computer algorithms that can improve automatically through experience. It can be divided in statistical and pattern recognition (Bayesian classifiers), inductive learning of symbolic rules (decision trees) and artificial neural networks (Kononenko, 2001).

To analyse a biomedical dataset we need five steps: (1) problem identification; (2) data extraction; (3) data pre-processing; (4) data mining, and (5) pattern interpretation and presentation (Lee & Abbott, 2003). Also, to be applied in medical diagnostic tasks it should fit some requirements (Kononenko, 2001):

- Good performance/high accuracy;
- Dealing with missing data;
- Dealing with error data;
- Transparency of diagnostic;
- Explanation ability;
- Reduction of the number of tests.

3.9.1 Bayesian networks

BN are important to machine learning because they provide a quantitative approach to assess the evidence supporting alternative and also represents a joint probability distribution and domain prior knowledge when analysing biomedical data (Lee & Abbott, 2003). BN are based on probability theory and are graph-based for the representation and manipulation of uncertain knowledge (P. Lucas, 2004). They are the most popular uncertainty formalism because it fills the requirements described above – handle noise and missing or error information, provide probabilistic relations with a good interface and can learn from the data and/or incorporate expert knowledge. That’s why it is becoming the most reliable technique for medical domain (Lee & Abbott, 2003).
Being a graphical representation of statistical dependences and independences among variables, BN deal with the direction of the arcs and the assumption that the classification of patterns is expressed in probabilistic terms between predictors and outcome variables. Each node represents a variable and each arc the (in) dependence of all its non-descendent nodes, given its parents. For building the BN, two phases are required: the creation of the BN structure and the assessment of prior and local condition probabilities (Lee & Abbott, 2003). We can build it manually or learn from data. The first one is time consuming and requires the access to human experts. The second one is much more attractive, being nowadays in constant use (P. J. F. Lucas et al., 2004). When using Bayesian network building from data we have to satisfy some requisites: unbiased data collection, variables and values should match characteristics in the network, the dataset size should allow reliable information of probabilistic relationships among variables. Regarding missing data we have to choose one of two options: we either remove all the cases with missing data or we fill/input missing data. The first one can lead to a loss of large number of valuable data, leading to a decrease in the robustness of the model. The other replaces the missing values with an estimate of the actual value (P. J. F. Lucas et al., 2004).

Naïve Bayes (NV) classifier is based on the simple assumption that the attribute values are conditionally independent given the target value. Tree augmented Bayesian network (TAN) is an extension of NV, reducing the number of independent assumptions, each node has at most two dependences, one conditionally from the class and other conditionally from another attribute. Hill climbing (HC) is an iterative algorithm that starts with an arbitrary solution to a problem, then attempts to find a better solution by incrementally changing a single element of the solution. If the change produces a better solution, an incremented change is made to the new solution, repeating until no further improvements can be found (P. J. F. Lucas et al., 2004).

The models/classifiers performance and quality should be evaluated by their ability of discrimination and calibration. Discrimination measures how the model is able to separate cases with positive outcome value from those with negative outcome value. Area under the ROC Curve (AUC) is the most common measure, plotting a sensitivity versus specificity model. On the other hand, calibration is how close the predicted values are to the real outcomes (Lee & Abbott, 2003).

Sensitivity can be defined as the number of correctly classified cases as positives divided by the total number of actual positive cases. Specificity is the number of correctly classified cases as negatives divided by the total number of actual negative cases (Lee & Abbott, 2003). Also, PPV and negative predictive value (NPV) should be reported in the results. PPV is the proportion of cases that the network classifies as positive that actually are positive and NPV is the proportion of cases that the network classifies as negative that actually are negative (Lee & Abbott, 2003).
4. Methods
4. Methods

4.1 Variables

A literature review was performed to define the most relevant variables to be collected. The search was performed on Pubmed on the 19th of April of 2015, using the Mesh terms “risk factors”, “sleep apnea, obstructive” and “diagnosis”. A total of 1397 articles were obtained, but we only selected reviews. At first we found 310 reviews, but we excluded 162 articles after reading the title and abstract. The exclusion criteria were: therapeutic or surgical studies, children, pregnant women, not related to risk factors and OSA as a secondary problem from another disease. In the end we had 148 articles to analyse the full text. In this second analysis we disqualified 46 (without access in time), 46 (not related to risk factors), 8 (not in English or Portuguese), keeping 48 articles.

Data was retrospectively collected from medical histories in the beginning of June, in a total of 39 variables collected and studied, presented below (Al Lawati, Patel, & Ayas, 2009; Ali et al., 2014; Andrews & Oei, 2004; Ayas et al., 2014; Bennett, 2014; Berry, 2008; Bonekat & Hardin, 2003; Bonsignore, Borel, Machan, & Grunstein, 2013; Brisco, Meredith; Goldberg, 2010; Doghramji, 2008; Eckert & Malhotra, 2008; Hanafy, 2007; Harris, Glozier, Ratnavadivel, & Grunstein, 2009; Heatley et al., 2013; Jordan & McEvoy, 2003; Kapur, 2010; Jamie C M Lam & Ip, 2010; Jamie C M Lam et al., 2010; Jamie Chung Mei Lam, Mak, & Ip, 2012; Loke, Brown, Kwok, Niruban, & Myint, 2012; Madani & Madani, 2009; Madani, 2007; Malhotra & White, 2002; Mannarino, Di Filippo, & Pirro, 2012; Martins, Maria, Pereira, & Moura, 2007; Mbata & Chukwuuka, 2012; Mieczkowski & Ezzie, 2014; Mohsenin, 2014; Pagel, 2008; Park, Ramar, & Olson, 2011; Pillar & Lavie, 2011; Riha, 2010; Salles, Cristina; Ramos, Regina; Machado, Adelmir; Cruz, 2013; Schwab, 2005; Schwartz et al., 2008; Sheldon, Belan, Neill, & Rowland; Smith, Ian; Quinnell, 2011; Stanke-Labesque, Pepin, Gautier-Veyret, Levy, & Back, 2014; Stierer & Punjabi, 2005; Sutherland, Lee, & Cistulli, 2012; Tasali, Mokhlesi, & Van Cauter, 2008; Tate & Tasota, 2002; Togeiro et al., 2010; Tregear, Reston, Schoelles, & Phillips, 2009; Tuomilehto, Seppi, & Uusitupa, 2013; Villaneuva, Buchanan, Yee, & Grunstein, 2005; Viswanath, Ramamurthy, Dinesh, & Srinivas, 2015; Younes, 2003).
• **Demographic variables:**
  - Gender;
  - Race;
  - Age.

• **Physical examination:**
  - Body mass index;
  - Neck circumference;
  - Abdominal circumference;
  - Craniofacial and upper airways abnormalities.

• **Clinical history:**
  - Daytime sleepiness;
  - Snoring;
  - Witnessed apneas;
  - Shocking/gasping;
  - Motor vehicle crashes;
  - Driver;
  - Refreshing sleep;
  - Restless sleep;
  - Humor alterations;
  - Nocturia;
  - Decreased libido;
  - Morning headaches;
  - Concentration decrease;
  - Alcohol;
  - Smoking;
  - Coffee;
  - Sedatives;
  - Genetics/Family history;
  - Epworth somnolence scale;
  - Apnea-hypopnea index.

• **Comorbidities:**
  - Atrial fibrillation;
  - Stroke;
  - Myocardial infarction;
  - Pulmonary hypertension;
  - Congestive heart failure;
  - Diabetes;
  - Dyslipidemia;
  - Renal failure;
  - Hypothyroidism;
  - Gastroesophageal reflux;
  - Hypertension;
  - Depression/anxiety.

### 4.2 Data collection

This study included patients referred to PSG at the Vila Nova de Gaia/Espinho Hospital Center, from 1st of January to 31st of May of 2015. The clinical data were extracted from the software SAM and directly from the database of the Sleep Laboratory. All the variables were checked to avoid missing information, but not all of the variables were completed, even though we had access to all of the information about each patient. All the diaries and final diagnosis of each patient, from different clinical sets, were obtained and analysed. In the case of missing data, we assumed that the answer is “No” because it is not described in the medical diaries.

The inclusion criteria were patients with more than 18 years old and suspicion of OSA. On the other hand, patients already diagnosed with OSA (performing therapeutic studies), patients with suspicion of another disease than OSA, patients with severe lung diseases or neurological condition, like neuromuscular diseases and pregnant women, were excluded.
The development of the models and its validation were performed in the total sample of 194 patients, after applying the inclusion and exclusion criteria (collected data from 241 patients). The outcome measure is the clinical diagnosis, categorized into normal or OSA (mild, moderate and severe).

This was approved by the Ethics Commission of Vila Nova de Gaia/Espinho Hospital Center, fulfilling the Declaration of Helsinki (annexe 1).

4.3 Bayesian networks

First, a pre-processing of the data was performed and non-continuous variables were categorized into dichotomous variables:

- **BMI**
  - BMI < 30 Kg/m - Normal
  - BMI ≥ 30 Kg/m - Obese

- **NC**
  - Female
    - ≤ 37 cm – Normal
    - > 37 cm – Increased
  - Male
    - ≤ 42 cm – Normal
    - > 42 cm – Increased

- **AC**
  - Female
    - ≤ 80 cm – Normal
    - > 80 cm – Increased
  - Male
    - ≤ 94 cm – Normal
    - > 94 cm – Increased

- **Age**
  - 0 to 39 years;
  - 40 to 49 years;
  - 50 to 59 years;
  - 60 to 69 years;
  - 70 to 79 years;
  - 80 to 89 years.

- **Smoking**
  - Yes
  - No
A statistical investigate of the previous work (OSA2012) referred in the chapter introduction was performed. All the 86 patients were analyse to be compare with the new dataset without missing values, using Chi-square test with a significance level of 5%.

The first BN models were built using all the 39 variables without missing values (OSA39). This dataset was used to learn the structure, fit the network (probabilities) and to calculate the predict values and also in cross-validation. The second BN models were built using only 13 variables (OSA13) that were considered significant, after performing Chi-square test, with a significance level of 5%. Also, the variables that have a p value below 0.200 and a value of n≥10 patients were also included. A logistic regression model – backward conditional - were calculated using 39 variables as independent variables and the presence of OSA as dependent variable, to helped construct the second model. These were performed in the “real” dataset, with the missing’s values.

We performed AUC to find the cut-off of each model and Receiver Operating Characteristics (ROC) curve analysis to determine prediction error. The target is 100% sensitivity, avoiding false negatives, with increasing specificity.

Given the previous good results in other clinical domains, we use NB and TAN to build the models. We use software R to learn the networks, with the packages foreign, bnlearn, gRain and pROC. SamIam software was used to consult the conditional probabilities, given the outcome.

In the cross-validation we used a 10 times 10-fold cross validation to check for external validation. All the analysis was performed with R software and SPSS software, version 22.

The following flow diagram illustrated all the steps take under consideration in the development of this dissertation (figure 1).
Figure 1: Dissertation Flow diagram

Step 1: Literature review
Step 2: 39 variables
Step 3: Data collection
Step 4: Dataset with missing’s
Step 5: Inclusion/Exclusion criteria
Step 6: Data pre-processing
Step 7: OSA39
Step 8: OSA2012
Step 9: New models
Step 10: OSA39 model
Step 11: OSA13 model
5. Results
5. Results

We considered for inclusion 241 patients, 47 were excluded for several reasons described in figure 1.

![Flow diagram for inclusion and exclusion criteria in the study](image)

In the 194 patients included 123 (63%) were male and 71 (37%) were women, with a mean age of 58 years old. Sixty six patients (34%) had normal result with a mean age of 50 years; of the 128 patients with OSA (66%), 63 (33%) categorized in mild, 32 (16%) in moderate and 33 (17%) in severe, the mean age was 62 years.

Table 1 described the first dataset obtained with the data collection, without the assumption of the data. This is considered the “real” dataset and for this reason, the
selection of the variables for the second BN were found here. Also the logistic regression were applied to this dataset.

Table 1: Description and Chi-square for the 39 variables without the assumption

<table>
<thead>
<tr>
<th>Gender, n (%)</th>
<th>Total (n=194)</th>
<th>OSA (n=128)</th>
<th>Normal (n=66)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>71 (37)</td>
<td>36 (28)</td>
<td>35 (53)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male</td>
<td>123 (63)</td>
<td>92 (72)</td>
<td>31 (47)</td>
<td></td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Caucasian</td>
<td>191 (99)</td>
<td>126 (98)</td>
<td>65 (99)</td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>3 (2)</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Age, mean (sd)</td>
<td>58 (13)</td>
<td>62 (11)</td>
<td>50 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, median (min-max)</td>
<td>29.5 (18.2-58.2)</td>
<td>30.0 (18.2-58.2)</td>
<td>28.6 (21.6-51.8)</td>
<td>0.229</td>
</tr>
<tr>
<td>NC, median (min-max)</td>
<td>42 (31-52)</td>
<td>42 (32-52)</td>
<td>40 (31-49)</td>
<td>0.051</td>
</tr>
<tr>
<td>AC, median (min-max)</td>
<td>107 (66-151)</td>
<td>108 (68-151)</td>
<td>105 (66-139)</td>
<td>0.560</td>
</tr>
<tr>
<td>CFA, n (%)</td>
<td>43 (22)</td>
<td>32 (97)</td>
<td>11 (79)</td>
<td>0.073</td>
</tr>
<tr>
<td>Snoring, n(%)</td>
<td>175 (90)</td>
<td>114 (97)</td>
<td>61 (100)</td>
<td>0.320</td>
</tr>
<tr>
<td>Witnessed apneas, n (%)</td>
<td>104 (54)</td>
<td>72 (75)</td>
<td>32 (60)</td>
<td>0.063</td>
</tr>
<tr>
<td>Choking, n (%)</td>
<td>76 (39)</td>
<td>49 (59)</td>
<td>27 (60)</td>
<td>0.916</td>
</tr>
<tr>
<td>Vehicle crashes, n (%)</td>
<td>6 (3)</td>
<td>2 (4)</td>
<td>4 (16)</td>
<td>0.083</td>
</tr>
<tr>
<td>Refreshing sleep, n (%)</td>
<td>45 (23)</td>
<td>31 (32)</td>
<td>14 (25)</td>
<td>0.363</td>
</tr>
<tr>
<td>Humor alterations, n (%)</td>
<td>2 (1)</td>
<td>1 (100)</td>
<td>1 (100)</td>
<td>NA</td>
</tr>
<tr>
<td>Nocturia, n (%)</td>
<td>70 (36)</td>
<td>53 (69)</td>
<td>17 (50)</td>
<td>0.058</td>
</tr>
<tr>
<td>Restless sleep, n (%)</td>
<td>76 (39)</td>
<td>48 (75)</td>
<td>28 (80)</td>
<td>0.573</td>
</tr>
<tr>
<td>Decreased libido, n (%)</td>
<td>18 (9)</td>
<td>13 (100)</td>
<td>5 (83)</td>
<td>0.316</td>
</tr>
<tr>
<td>Morning headaches, n (%)</td>
<td>66 (34)</td>
<td>44 (61)</td>
<td>22 (55)</td>
<td>0.529</td>
</tr>
<tr>
<td>Alcohol consumption, n (%)</td>
<td>96 (50)</td>
<td>65 (66)</td>
<td>31 (53)</td>
<td>0.102</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32 (17)</td>
<td>20 (17)</td>
<td>12 (19)</td>
<td>0.525</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>56 (29)</td>
<td>40 (33)</td>
<td>16 (25)</td>
<td></td>
</tr>
<tr>
<td>Use sedatives, n (%)</td>
<td>50 (26)</td>
<td>27 (96)</td>
<td>23 (89)</td>
<td>0.342</td>
</tr>
<tr>
<td>ESS, median (min-max)</td>
<td>11 (0-24)</td>
<td>10 (0-23)</td>
<td>13 (0-24)</td>
<td>0.002</td>
</tr>
<tr>
<td>Concentration decrease, n (%)</td>
<td>42 (22)</td>
<td>20 (43)</td>
<td>22 (71)</td>
<td>0.014</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>15 (8)</td>
<td>15 (31)</td>
<td>0 (0)</td>
<td>0.008</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>17 (9)</td>
<td>14 (29)</td>
<td>3 (12)</td>
<td>0.109</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>14 (7)</td>
<td>12 (26)</td>
<td>2 (9)</td>
<td>0.198</td>
</tr>
<tr>
<td>Pulmonary hypertension, n (%)</td>
<td>1 (1)</td>
<td>1 (50)</td>
<td>0 (0)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>20 (10)</td>
<td>16 (28)</td>
<td>4 (17)</td>
<td>0.277</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>47 (24)</td>
<td>33 (72)</td>
<td>14 (74)</td>
<td>0.873</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>99 (51)</td>
<td>76 (95)</td>
<td>23 (89)</td>
<td>0.359</td>
</tr>
<tr>
<td>Renal failure, n (%)</td>
<td>3 (2)</td>
<td>2 (33)</td>
<td>1 (25)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Hypothyroidism, n (%)</td>
<td>2 (1)</td>
<td>1 (50)</td>
<td>1 (25)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Gastroesophageal reflux, n (%)</td>
<td>3 (2)</td>
<td>2 (22)</td>
<td>1 (20)</td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>
### Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=194)</th>
<th>OSA (n=128)</th>
<th>Normal (n=66)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension, n (%)</td>
<td>123 (63)</td>
<td>91 (96)</td>
<td>32 (89)</td>
<td>0.214</td>
</tr>
<tr>
<td>Driver, n (%)</td>
<td>16 (8)</td>
<td>13 (12)</td>
<td>3 (5)</td>
<td>0.130</td>
</tr>
<tr>
<td>Coffee, n (%)</td>
<td>120 (62)</td>
<td>76 (88)</td>
<td>44 (85)</td>
<td>0.525</td>
</tr>
<tr>
<td>Daytime sleepiness, n (%)</td>
<td>114 (59)</td>
<td>65 (77)</td>
<td>49 (94)</td>
<td>0.010</td>
</tr>
<tr>
<td>Genetics/Family history, n (%)</td>
<td>2 (1)</td>
<td>0 (0.0)</td>
<td>2 (100)</td>
<td>0.333</td>
</tr>
<tr>
<td>Depression, n (%)</td>
<td>53 (27)</td>
<td>28 (97)</td>
<td>25 (93)</td>
<td>0.605</td>
</tr>
<tr>
<td>AHIs, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>66 (34)</td>
<td></td>
<td>35 (53)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>63 (33)</td>
<td></td>
<td>31 (47)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>32 (16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>33 (17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSA, n (%)</td>
<td>128 (66)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI: Body Mass Index; NC: Neck circumference; AC: Abdominal circumference; CFA: Craniofacial and upper airway abnormalities; ESS: Epworth Somnolence Scale; AHI: Apnea-Hypopnea Index; OSA: Obstructive Sleep Apnea

After this analysis, the dataset was fulfilling with the assumption. Like previous statement, the access to all the diaries and diagnostics of each patient were obtained and studied, so we assumed that if the patient does not have a medical record saying yes, is because he or she does not have it. After this assumption, table 2 demonstrated the new dataset obtained.

**Table 2: Description and Chi-square for the 39 variables with the assumption**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=194)</th>
<th>OSA (n=128)</th>
<th>Normal (n=66)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>71 (37)</td>
<td>36 (28)</td>
<td>35 (53)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male</td>
<td>123 (63)</td>
<td>92 (72)</td>
<td>31 (47)</td>
<td></td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Caucasian</td>
<td>191 (99)</td>
<td>126 (98)</td>
<td>65 (99)</td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>3 (2)</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Age, mean (sd)</td>
<td>58 (13)</td>
<td>62 (11)</td>
<td>50 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, median (min-max)</td>
<td>29.5 (18.2-58.2)</td>
<td>30.0 (18.2-58.2)</td>
<td>28.6 (21.6-51.8)</td>
<td>0.229</td>
</tr>
<tr>
<td>NC, median (min-max)</td>
<td>42 (31-52)</td>
<td>42 (32-52)</td>
<td>40 (31-49)</td>
<td>0.051</td>
</tr>
<tr>
<td>AC, median (min-max)</td>
<td>107 (66-151)</td>
<td>108 (68-151)</td>
<td>105 (66-139)</td>
<td>0.560</td>
</tr>
<tr>
<td>CFA, n (%)</td>
<td>43 (22)</td>
<td>32 (25)</td>
<td>11 (17)</td>
<td>0.186</td>
</tr>
<tr>
<td>Snoring, n(%)</td>
<td>175 (90)</td>
<td>114 (89)</td>
<td>61 (92)</td>
<td>0.455</td>
</tr>
<tr>
<td>Witnessed apneas, n (%)</td>
<td>104 (54)</td>
<td>72 (56)</td>
<td>32 (49)</td>
<td>0.304</td>
</tr>
<tr>
<td>Choking, n (%)</td>
<td>76 (39)</td>
<td>49 (38)</td>
<td>27 (41)</td>
<td>0.722</td>
</tr>
<tr>
<td>Vehicle crashes, n (%)</td>
<td>6 (3)</td>
<td>2 (2)</td>
<td>4 (6)</td>
<td>0.183</td>
</tr>
<tr>
<td>Refreshing sleep, n (%)</td>
<td>45 (23)</td>
<td>31 (24)</td>
<td>14 (21)</td>
<td>0.638</td>
</tr>
<tr>
<td>Humor alterations, n (%)</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Nocturia, n (%)</td>
<td>70 (36)</td>
<td>53 (41)</td>
<td>17 (26)</td>
<td>0.032</td>
</tr>
<tr>
<td>Restless sleep, n (%)</td>
<td>76 (39)</td>
<td>48 (38)</td>
<td>28 (42)</td>
<td>0.506</td>
</tr>
<tr>
<td>Decreased libido, n (%)</td>
<td>18 (9)</td>
<td>13 (10)</td>
<td>5 (8)</td>
<td>0.557</td>
</tr>
</tbody>
</table>
The OSA39 were used to construct the two BN models, like previous said, and so is this that we needed to use to compared the new data and the old one. This comparison was relevant because we wanted to expand our results. Table 3 is the result of the comparison of OSA39 and OSA2012.
Table 3: Comparison of the new dataset (OSA39) with the previous work (OSA2012)

<table>
<thead>
<tr>
<th></th>
<th>OSA39 (n=194)</th>
<th>OSA2012 (n=86)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>71 (37)</td>
<td>16 (19)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>Male</td>
<td>123 (63)</td>
<td>70 (81)</td>
<td></td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>191 (99)</td>
<td>84 (98)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>African</td>
<td>3 (2)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td><strong>Age, mean (sd)</strong></td>
<td>58 (13)</td>
<td>56 (14)</td>
<td>0.676</td>
</tr>
<tr>
<td><strong>BMI, median (min-max)</strong></td>
<td>29.5 (18.2-58.2)</td>
<td>28.9 (21.7-44.5)</td>
<td><strong>0.012</strong></td>
</tr>
<tr>
<td><strong>NC, median (min-max)</strong></td>
<td>42 (31-52)</td>
<td>41 (33-104)</td>
<td>0.074</td>
</tr>
<tr>
<td><strong>AC, median (min-max)</strong></td>
<td>107 (66-151)</td>
<td>103 (2-150)</td>
<td>0.201</td>
</tr>
<tr>
<td><strong>CFA, n (%)</strong></td>
<td>43 (22)</td>
<td>46 (54)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td><strong>Snoring, n(%)</strong></td>
<td>175 (90)</td>
<td>86 (100)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td><strong>Witnessed apneas, n (%)</strong></td>
<td>104 (54)</td>
<td>55 (65)</td>
<td>0.085</td>
</tr>
<tr>
<td><strong>Choking, n (%)</strong></td>
<td>76 (39)</td>
<td>22 (26)</td>
<td><strong>0.028</strong></td>
</tr>
<tr>
<td><strong>Vehicle crashes, n (%)</strong></td>
<td>6 (3)</td>
<td>6 (8)</td>
<td>0.112</td>
</tr>
<tr>
<td><strong>Refreshing sleep, n (%)</strong></td>
<td>45 (23)</td>
<td>39 (45)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td><strong>Humor alterations, n (%)</strong></td>
<td>2 (1)</td>
<td>4 (5)</td>
<td>0.074</td>
</tr>
<tr>
<td><strong>Nocturia, n (%)</strong></td>
<td>70 (36)</td>
<td>32 (37)</td>
<td>0.857</td>
</tr>
<tr>
<td><strong>Restless sleep, n (%)</strong></td>
<td>76 (39)</td>
<td>13 (15)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td><strong>Decreased libido, n (%)</strong></td>
<td>18 (9)</td>
<td>1 (1)</td>
<td><strong>0.013</strong></td>
</tr>
<tr>
<td><strong>Morning headaches, n (%)</strong></td>
<td>66 (34)</td>
<td>18 (21)</td>
<td><strong>0.027</strong></td>
</tr>
<tr>
<td><strong>Alcohol consumption, n (%)</strong></td>
<td>96 (50)</td>
<td>38 (44)</td>
<td>0.413</td>
</tr>
<tr>
<td><strong>Smoking, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32 (17)</td>
<td>17 (20)</td>
<td>0.743</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>56 (29)</td>
<td>22 (26)</td>
<td>0.277</td>
</tr>
<tr>
<td><strong>Use sedatives, n (%)</strong></td>
<td>50 (26)</td>
<td>17 (20)</td>
<td></td>
</tr>
<tr>
<td><strong>ESS, median (min-max)</strong></td>
<td>11 (0-24)</td>
<td>9 (0-24)</td>
<td><strong>0.044</strong></td>
</tr>
<tr>
<td><strong>Concentration decrease, n (%)</strong></td>
<td>42 (22)</td>
<td>11 (13)</td>
<td>0.081</td>
</tr>
<tr>
<td><strong>Atrial fibrillation, n (%)</strong></td>
<td>15 (8)</td>
<td>2 (2)</td>
<td>0.081</td>
</tr>
<tr>
<td><strong>Stroke, n (%)</strong></td>
<td>17 (9)</td>
<td>3 (4)</td>
<td>0.114</td>
</tr>
<tr>
<td><strong>Myocardial infarction, n (%)</strong></td>
<td>14 (7)</td>
<td>6 (7)</td>
<td>0.943</td>
</tr>
<tr>
<td><strong>Pulmonary hypertension, n (%)</strong></td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td><strong>Congestive heart failure, n (%)</strong></td>
<td>20 (10)</td>
<td>1 (1)</td>
<td><strong>0.007</strong></td>
</tr>
<tr>
<td><strong>Diabetes, n (%)</strong></td>
<td>47 (24)</td>
<td>17 (20)</td>
<td>0.412</td>
</tr>
<tr>
<td><strong>Dyslipidemia, n (%)</strong></td>
<td>99 (51)</td>
<td>1 (1)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td><strong>Renal failure, n (%)</strong></td>
<td>3 (2)</td>
<td>0 (0)</td>
<td>0.555</td>
</tr>
<tr>
<td><strong>Hypothyroidism, n (%)</strong></td>
<td>2 (1)</td>
<td>3 (4)</td>
<td>0.328</td>
</tr>
<tr>
<td><strong>Gastroesophageal reflux, n (%)</strong></td>
<td>3 (2)</td>
<td>4 (5)</td>
<td>0.207</td>
</tr>
<tr>
<td><strong>Hypertension, n (%)</strong></td>
<td>123 (63)</td>
<td>42 (49)</td>
<td><strong>0.022</strong></td>
</tr>
<tr>
<td><strong>Driver, n (%)</strong></td>
<td>16 (8)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Coffee, n (%)</strong></td>
<td>120 (62)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Daytime sleepiness, n (%)</td>
<td>Genetics/Family history, n (%)</td>
<td>Depression, n (%)</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------------</td>
<td>--------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td></td>
<td>124 (64)</td>
<td>2 (1)</td>
<td>54 (28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>66 (34)</td>
<td>63 (33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>39 (39)</td>
<td>18 (21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>54 (16)</td>
<td>15 (17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33 (17)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

BMI: Body Mass Index; NC: Neck circumference; AC: Abdominal circumference; CFA: Craniofacial and upper airway abnormalities; ESS: Epworth Somnolence Scale; AHI: Apnea-Hypopnea Index; OSA: Obstructive Sleep Apnea

Analysing table 3, becomes obvious that the two datasets are not resembling. Because of this, the results of this dissertation will only rely on the new dataset.

Utilizing R software two BN models were created for the 39 variables. The first (figure 3) is a NB model, with the outcome – OSA – and all the factors. The second image is regarding a TAN model (figure 4).

![Figure 3: Naive Bayes with the 39 variables](image-url)
For these two models we obtained a ROC curve (figure 5), demonstrated and AUC of 83% for the NB model (NB39) and 97% for the TAN (TAN39). When performing predict and cross-validation we obtained a sensitivity of 75% and a specificity of 57% for the NB model and 82% and 55%, respectively, for TAN (table 4).

![Figure 4: Tree augmented Bayesian network with the 39 variables](image)

![Figure 5: ROC Curves for Naive Bayes and Tree augmented Bayesian network with the 39 variables](image)

Figure 4: Tree augmented Bayesian network with the 39 variables

Figure 5: ROC Curves for Naive Bayes and Tree augmented Bayesian network with the 39 variables
Although the values of ROC curves are higher than 80% presented good discriminate power towards the outcome (using the 50% threshold classification cut off to predict the outcome) the specificity of the models are low. On the other hand, if we try to apply the TAN39 to the clinical setting we will have a problem: the number of variables to be collected. Thinking of this issue, a new model were created. This will only involve 13 variables, become easiest to fulfilling.

Analysing table 1 informed us of the 14 variables that are relevant to the model: gender; age; NC; craniofacial and upper airway abnormalities; WA; nocturia; alcohol before sleep; ESS; concentration decrease; atrial fibrillation; stroke; myocardial infarction; driver (truck) and daytime sleepiness. But, after the logistic regression and analyse of the TAN network, we considered age as a confounding factor.

Figure 6 presents the NB with the 13 variables selected (NB13).

For the 13 variables, ROC curve (figure 7), demonstrated an AUC of 79% for the NB model (NB13) and 85% for the TAN (TAN13).
The figure 8 demonstrated the TAN network obtained. And figure 9, the conditional probabilities of this network.

Figure 8: Tree augmented Bayesian network with the 13 variables selected

Figure 9: Marginal probabilities of Tree augmented Bayesian network to the presence of OSA
The 13 variables selected can be divided into risk factors and diagnostic factors. This can be relevant if we want to study a causal model. In the risk factors group, we may include: gender; NC; craniofacial and upper airway abnormalities; alcohol before sleep; atrial fibrillation; stroke; myocardial infarction and truck driver. In the diagnostic factors: WA; nocturia; ESS; concentration decrease and daytime sleepiness. A BN model was created to illustrate this, using HC strategy.

![Figure 10: Causal Hill climbing with the 13 variables selected](image)

Table 4 presents the result of the 10-times-repeated stratified 10-fold cross-validation. From the exposed results, TAN39 rises as the best classification model (using the 50% threshold classification cut off to predict the outcome) only losing in terms of specificity. This could possibly be overcome with a threshold study.

<table>
<thead>
<tr>
<th>Model</th>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Precision (Positive)</th>
<th>Precision (Negative)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NB39</td>
<td>68.82%</td>
<td>75.03%</td>
<td>56.67%</td>
<td>77.81%</td>
<td>54.46%</td>
<td>71.61%</td>
</tr>
<tr>
<td></td>
<td>[66.67,70.97]</td>
<td>[72.57,77.5]</td>
<td>[52.46,60.87]</td>
<td>[75.97,79.66]</td>
<td>[51.03,57.88]</td>
<td>[68.88,74.33]</td>
</tr>
<tr>
<td>TAN39</td>
<td>72.57%</td>
<td>81.67%</td>
<td>54.83%</td>
<td>78.5%</td>
<td>62.46%</td>
<td>78.6%</td>
</tr>
<tr>
<td></td>
<td>[70.69,74.45]</td>
<td>[79.26,84.08]</td>
<td>[50.93,58.74]</td>
<td>[76.93,80.07]</td>
<td>[58.67,66.25]</td>
<td>[76.4,80.8]</td>
</tr>
<tr>
<td>NB13</td>
<td>68.84%</td>
<td>75.8%</td>
<td>55.25%</td>
<td>77.31%</td>
<td>55.46%</td>
<td>74.58%</td>
</tr>
<tr>
<td></td>
<td>[66.84,70.83]</td>
<td>[73.43,78.17]</td>
<td>[51.56,58.94]</td>
<td>[75.62,79]</td>
<td>[52.08,58.84]</td>
<td>[72.2,76.96]</td>
</tr>
<tr>
<td>TAN13</td>
<td>69.9%</td>
<td>81.22%</td>
<td>47.75%</td>
<td>75.54%</td>
<td>58.64%</td>
<td>75.47%</td>
</tr>
<tr>
<td></td>
<td>[68.01,71.79]</td>
<td>[79.83,83.43]</td>
<td>[44.28,51.22]</td>
<td>[74.14,76.94]</td>
<td>[54.58,62.7]</td>
<td>[73.01,77.93]</td>
</tr>
</tbody>
</table>
6. Discussion
6. Discussion

The initial step towards defining a decision support tool is to evaluate the need for it. Previous work on BN for OSA was biased by a selection of significant variables (gender, BMI, NC, AC, WA and alcohol before sleep). This reduced the interpretability and discriminative power of the models and the predictive quality.

In the sample, the proportion of normal results was 34%, revealing a large number of normal exams that are performed every day. As we expected, a good clinical decision support tool is needed to prioritize patients (reducing the waiting lists).

A large number of clinical variables were used (39 variables), but only 13 had significant results: gender, age, NC, craniofacial and upper airway abnormalities, WA, nocturia, alcohol before sleep, ESS, concentration decrease, atrial fibrillation, stroke, myocardial infarction, truck driver and daytime sleepiness.

In our study, male gender was more prevalent (63%), as referred in the background. One possible explanation is the higher prevalence of craniofacial and upper airway abnormalities (21%), and also snoring (90%). Regarding the WA, men have a percentage of 60% against 43% in women. This can be explain because of female bed partners appear to have a lower threshold for symptom perceptions and reporting than male bed partners. Other studies presents age as an important risk factor. In our study, even though age presents a statistical significance, it cannot be used, because was considered a confounding factor. The NC need to be consider as an important factor to OSA, and more studies are important to prove this.

In the first BN model (39 variables), a sensitivity of 82% and a PPV of 79% were reach with the TAN model, telling us that patients with OSA are identified in 80% of the exams performed. It left us a 20% of patients that have the disease and the BN model cannot predict it. In the second BN model (13 variables), a sensitivity of 81% and a PPV of 76% were obtained, also in TAN model. Looking to the AUC of each model – TAN 39 and TAN13 – with 79% and 75%, respectively, we can affirm that the selection of the variables, making the model more adequate to the clinical practice, can be generalized.

To explain how the TAN13 network can be implemented in a clinical decision support tool, we apply information of several patients (marked in red).
The first patient is female and have a normal NC. Is a health patient, so thus not have any comorbidity or WA. She described fatigue and presents an ESS of 11. She do not have the drivers licence and usually do not go to the bathroom during the night. Regarding alcohol consumption, she does not drink alcohol. The probability of OSA is 28% (figure 11). The same characteristics, but in a male, the probability of OSA increases for 59% (figure 12).

Figure 12: Inference using TAN13 in a female patient

Figure 11: Inference using TAN13 in a male patient
Imagine that, in the case that we presented above, we don’t access to NC. We can use TAN13 without this information as the probabilities are obtained are based on the learning process that the network are built with the information of other patients, in this case, with 194 other patient’s. The results of this missing value are present below in figure 13. In the female case the probability changes to 34% and in the male case to 65%.

Figure 13: Inference using TAN13 in female and male patient
6.1 Limitations

The lack of representativeness of some factors, like ethnicity, vehicle crashes, humor alterations, decreased libido, pulmonary hypertension, congestive heart failure, renal failure, hypothyroidism, gastroesophageal reflux and genetics, may lead to a biased model in the 39 variables. Our study was conducted on patients referred by primary care physicians to the sleep consult, so OSA prevalence cannot be estimated.

The selection of significant variables (13 variables) may reduce the interpretability, the accuracy, sensitivity and precision of the model, but can improve the implementation of this network in the clinical practice.
7. Conclusion
7. Conclusion

Our study presents as main risk factors the gender; NC; craniofacial and upper airway abnormalities; alcohol before sleep; atrial fibrillation; stroke; myocardial infarction and truck driver. And as diagnostic factors the WA; nocturia; ESS; concentration decrease and daytime sleepiness.

We used two datasets. The first with the missing values, obtained directly from the diaries and diagnostics of each patient and the second one, using the first, but fulfilling the missing values with the assumption that if it was not described in the patient medical records, the patient does not get it. The first dataset is consider the “real” dataset and because of that this was used to test the Chi-square, and to obtain the significant variables. The second dataset were used to build the network.

Two types of models were created: NB and TAN. In our study, TAN is consider a better classifier, proving the great advantages of BN models. It can deal with missing information and its graphical representation can shows not only the probabilities given the patient characteristics but also the relationship between variables.

Portugal does not have a validated method to screen patients with suspicion of OSA, before performing PSG, so we think that our model (TAN13) consist in a valid method. A protocol of the evaluation of the implementation of TAN13 in the primary care are in the section annexe. We think that this can reduce the number of normal results exams, optimizing the available resources and prioritizing patients.
8. Future work
8. Future work

More studies are required to better fit a clinical decision support model into clinical practice, especially if we consider anticipating support to the primary care. We need to compare our results to other sleep laboratories, collected more information from risk and diagnostic factors and try to implement our protocol. This will be essentially to evaluate model TAN13 in the primary care.

Also, another variable to take into account would be Modified Mallampati. Nowadays, literature begins to talk about this as a risk factor for OSA. This is used to predict the ease of intubation. A high Mallampati score (>3) is associated with more difficult intubation as well as a higher incidence of OSA. It assesses the height of the mouth and the distance from the tongue base to the roof of the mouth.
9. References
9. References


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10. Annexes
Authorization for study realization

Projecto de Investigação "Bayesian network in obstructive sleep apnea"

Júlio Alberto Sampaio <sampaio@chvng.min-saude.pt> 17 de abril de 2015 às 10:35
Para: "ferneiradessantos.daniela@gmail.com" <ferneiradessantos.daniela@gmail.com>

Exma. Sr.*

Daniela Filipe Ferreira dos Santos

Informo que o pedido de autorização para a realização do Projecto de Investigação "Bayesian network in obstructive sleep apnea", foi autorizado pela Direção Clínica deste Centro Hospitalar.

Com os melhores cumprimentos,

Júlio Alberto Sampaio
Responsável Serviço
Centro de Formação e Ensino

Serviço de Formação, Ensino e Investigação

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