

# Identifying Patients At Risk For Obstructive Sleep Apnea In Primary Health Care : Can Obesity In Combination With Other High-risk Diagnoses Be Used For Screening Purposes?

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IDENTIFYING PATIENTS AT RISK FOR OBSTRUCTIVE SLEEP APNEA IN PRIMARY  
HEALTH CARE: CAN OBESITY IN COMBINATION WITH OTHER HIGH-RISK  
DIAGNOSES BE USED FOR SCREENING PURPOSES?

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## ABSTRACT

Obstructive sleep apnea (OSA) affects about 15 million adults in the United States, and is an independent risk factor for all-cause mortality. The under-diagnosing of OSA has been linked to the inadequate screening by primary care practitioners (PCPs). Existing screening tools are not widely used by PCPs possibly due to time constraints they experience as providers. This study demonstrates how common high-risk diagnoses (obesity, hypertension, diabetes mellitus type 2, dyslipidemia, arrhythmia, and coronary artery disease) can be used to help PCPs identify adult patients at risk for OSA. Unlike other screening tools, these diagnoses are easy to identify in a routine visit. This study was a retrospective chart review that used a random sample of 220 electronic health records. Seventy percent of the sample was positive for OSA, 69% had obesity, and 33% had two or more high-risk diagnoses. The setting of this study was six sleep centers located in five cities in Central Florida. Logistic regression was used to analyze the data to determine interaction among variables and odds ratios. The variables “obesity” and “two or more high-risk diagnoses” had significant effects on the likelihood of being diagnosed with OSA independently of each other (odds ratio of 4.2 and 4.3 respectively;  $p < .001$ ). However, there was no significant interaction between these two variables ( $p = .56$ ). The predictive value for an OSA diagnosis using “obesity” was 83%, and it was 88% using “two or more high-risk diagnoses.” These findings argue for the use of high-risk diagnoses to identify patients at risk for OSA. PCPs are in an ideal position to increase the number of patients screened and treated for OSA because they routinely see patients with these diagnoses in their practices. Proper diagnosis and treatment of OSA has the potential to improve patients’ outcomes and their quality of life.

I dedicate this Doctoral Dissertation to my family who made me believe I was capable of accomplishing this endeavor. I owe my deepest gratitude to my husband *Wilson* who has encouraged and supported my dreams for over 27 years. He has demonstrated his love in many ways, like the many bouquets of roses he gave me without any special reason while I was doing this research; sometimes he just sensed I needed them. I am most grateful for my son *Wilcley*; he has dedicated more time helping me throughout this thesis than any other person. His insight and feedback in editing, reviewing, and in the data analysis was crucial. I appreciate his generous support while he was busy finishing his own graduate studies and managing his business. My son *Wesley* has always had an encouraging word when I needed the most. He has been a blessing to me helping in technical issues and with the data analysis brainstorm. My daughter *Nathalia* has been a great source of inspiration to me. She has uplifted me and made me feel invincible when I faced the challenges along this journey. Her commitment to her goals and her ability to overcome obstacles has been a great example for me. My youngest teenager son *Wilson* has helped me in many ways, including setting up my new laptop when the old one crashed while I was in the process of collecting the data for this thesis. I knew I could always count on his amazing ingenuity and excellent technical skills. I also have sincere gratitude for the awesome parents I have who shaped the person I am today. My father *João* has made me believe since I was a little girl that I was created for a great purpose and that I could reach any dream I could dream. My mother *Zelina* is an example of a true achiever despite the circumstances. Her unselfish love for me goes beyond imagination. Above all, I give my deepest gratitude to *God* who made possible the impossible. I give to Him all the honor and glory for the work he allowed me to accomplish. “I can do all things through Christ which strengtheneth me” (Philippians 4:13, King James Version).

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“Don't be afraid to give your best to what seemingly are small jobs. Every time you conquer one it makes you that much stronger. If you do the little jobs well, the big ones will tend to take care of themselves.” - Dale Carnegie, 1936

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“What we can or cannot do, what we consider possible or impossible, is rarely a function of our true capability. It is more likely a function of our beliefs about who we are.” - Anthony Robbins, 1987

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## CHAPTER 1: INTRODUCTION

Obstructive sleep apnea (OSA) is a potentially disabling condition that if left untreated can have life-threatening consequences. OSA is an independent risk factor for all-cause mortality (Marshall et al., 2008). It negatively affects several health conditions and quality of life (Devulapally, Pongonis, & Khayat, 2009; Somers et al., 2008). Despite the severe effects of untreated OSA, it has a history of being under-diagnosed worldwide (Punjabi, 2008). Primary care practitioners (PCPs) are in a key position to identify OSA high-risk patients. However, poor screening in a primary health care (PHC) setting has been linked to the under-diagnosing of OSA (S. A. Chung, Jairam, Hussain, & Shapiro, 2002; Dodson, 2008; P. Lavie, 2006; Merritt, 2004; Reuveni et al., 2004; Skjodt, 2008). Patients usually present for routine consultation in a PHC setting for common health issues, some of which might be related to OSA. A few screening tools are available for evaluation of OSA high-risk, but they are not widely used in PHC settings (Khasawneh et al., 2009; McNicholas, 2008). This may be due to PCPs' unfamiliarity with these screening tools or due to time constraints. The purpose of this study is to demonstrate how the different combinations of common diagnoses such as obesity, hypertension, diabetes mellitus type 2, arrhythmia, and coronary artery disease can be used to help PCPs to identify OSA high-risk patients. Unlike some screening tools, these combinations of diagnoses are easy to identify in a routine PHC visit and do not require extra assessment or documentation. PCPs may find it useful to have a fast and simple way to determine, with a reasonable degree of certainty, which patients to send for a polysomnogram, a test that is used to diagnose OSA. If a sensitive screen could be developed that is based on combinations of diagnoses, PCPs could be able to diagnose and treat more patients for OSA.

## **Problem Background**

Obstructive Sleep Apnea (OSA) is a disorder affecting an estimated 15 million adults in the United States (F. Chung et al., 2008a; Somers et al., 2008). However, over 85% of people with OSA are not diagnosed. OSA is characterized by repeated episodes of nocturnal apnea and or hypopnea associated with hypoxemia. The repeated hypoxemia may produce sleep fragmentation causing daytime excessive sleepiness, cognitive dysfunction, and reduced vitality (Eckert & Malhotra, 2008; Gurubhagavatula, Nkwuo, Maislin, & Pack, 2008).

## **Obesity, Hypertension, and OSA**

Obesity is the number one risk factor for OSA (Devulapally et al., 2009) and is associated with a four-fold increase in prevalence of OSA (Somers et al., 2008). Coincidentally, 70% of OSA patients are obese (Wolk, Shamsuzzaman, & Somers, 2003). According to the 2009 self-reported adult obesity survey, the prevalence of adult obesity in the United States was 26.7% (Sherry, Blanck, Galuska, Pan, & Dietz, 2010). This prevalence was over 30% for the middle-aged population alone. Overall, the incidence of obesity has more than doubled in the United States over the last 30 years (Center for Disease Control and Prevention (CDC). Division of Nutrition, Physical Activity and Obesity, National Center for Chronic Disease Prevention and Health Promotion, 2010); therefore, more individuals are at risk for OSA.

The Joint National Committee guidelines identify OSA as one of the major causes of secondary hypertension (US Department of Health and Human Services. National Institute of Health. National Heart, Lung, and Blood Institute Committee, 2003). Hypertension and OSA are common comorbidities with about 50% of individuals with OSA being hypertensive and about

30% of hypertensive individuals having OSA (Devulapally et al., 2009; Somers et al., 2008).

Hence, individuals diagnosed with hypertension may also be at risk for OSA.

### **Health and Quality of Life**

The proper treatment of OSA has been linked to improvement of several health conditions and overall quality of life. The frequency with which these benefits are observed varies with pre-existing conditions in the individual patient. Nevertheless, examples in the literature of these benefits include the following: (1) decreased cardiovascular morbidity and improved management of cardiac arrhythmia, arterial hypertension, and pulmonary hypertension (Dodson, 2008; Kapur, Resnick, & Gottlieb, 2008; Merritt, 2004; Somers et al., 2008); (2) decreased exacerbation of depressive symptoms (Cross et al., 2008; D. J. Schwartz & Karatinos, 2007); (3) decreased postoperative complications (F. Chung et al., 2008a; Lopez, Stefan, Schulman, & Byers, 2008; Shafazand, 2009); (4) improved response in treatment of primary headaches (Rains & Poceta, 2006); (5) decreased sickness-absence at work (Westerlund et al., 2008); and (6) decreased motor vehicle accidents by reducing daytime sleepiness (S. A. Chung et al., 2002; Dodson, 2008; Doghramji, 2008; Lopez et al., 2008; Pack, Platt, & Pien, 2008; Reuveni et al., 2004).

### **Cost**

The overall cost of OSA is similar to other chronic diseases (AlGhanim et al., 2008). While the precise economic burden of OSA is difficult to measure, there is substantial evidence demonstrating the significant costs associated with this condition. For example, several studies have demonstrated the economic burden associated with untreated OSA, including health care

cost and motor vehicle accidents (AlGhanim, Comondore, Fleetham, Marra, & Ayas, 2008; Gurubhagavatula et al., 2008; Kapur, 2010; Sassani et al., 2004). Pagel (2008) did a controlled analysis and found hospital stay reduction from 1.27 days/year before diagnosis of OSA to 0.54 days/year after one year of treatment. These results translate to 42% reduction in hospital utilization after one year of treatment. With respect to road collisions, U.S. data from the year 2000 estimate costs directly related to OSA to be nearly \$16 billion in this country alone (Pagel, 2008).

### **Purpose of Study**

This study aims to investigate the effect of obesity in combination with other high-risk diagnoses (hypertension, diabetes mellitus type 2, dyslipidemia, arrhythmias, and coronary artery disease) in predicting the risk for diagnosis of OSA. The overwhelming number of patients with undiagnosed OSA can be related to poor screening in the PHC setting (S. A. Chung et al., 2002; Dodson, 2008; P. Lavie, 2006; Merritt, 2004; Reuveni et al., 2004; Skjodt, 2008). The use of screening tools such as the Epworth Sleepiness Scale, STOP-BANG, and the Berlin questionnaire are very helpful in proper identification of high-risk patients. However, many PCPs may not be familiar with these screening tools or may not find the time to use them, thus contributing to the under-diagnosis of OSA. The identification of high-risk diagnoses may be a fast and simple way for PCPs to identify the patients at risk for OSA because they see patients with these common diagnoses on a daily basis. Therefore, PCPs may feel more confident in ordering a polysomnogram for diagnosis of OSA for those patients identified as having particular combinations of high-risk diagnoses. Specifically, this study addresses the following research question: What is the effect of obesity in combination with one as compared to two or more other

high-risk diagnoses on the likelihood of being diagnosed with obstructive sleep apnea in a primary health care setting?

## Definitions

### Obstructive Sleep Apnea

Obstructive Sleep Apnea (OSA) is a disorder characterized by repeated episodes of apnea and or hypopnea associated with hypoxemia during sleep. It is related to a narrowing airway, decreased tone of the pharyngeal dilator muscles, or increased compliance of upper airway tissues (Somers et al., 2008). *Apnea* is considered a 10 second or greater pause in respiration due to a collapse of the pharyngeal airway. *Hypopnea* is a decrease in respiration associated with a fall in oxygen saturation by 4% from the patient's baseline. The number of apneas and hypopneas per hour of sleep designate the apnea-hypopnea index (AHI) (Somers et al., 2008), which is determined by a polysomnogram. The American Academy of Sleep Medicine, Task Force (2009), developed clinical guideline for evaluation and management of OSA in adults. The Task Force defined OSA as the presence of five or more AHI or respiratory disturbance index (RDI) when the patient presents daytime sleepiness, fatigue, sleep disturbance, waking up gasping for air, or loud snoring. Also, in the absence of symptoms, the diagnosis of OSA is granted when AHI or RDI is equal or greater than 15 (Epstein et al., 2009). The severity levels of OSA are related to the AHI or RDI score: 5-14 mild, 15-29 moderate, 30 or more severe (American Academy of Sleep Medicine Task Force, 1999; Epstein et al., 2009; Young, Peppard, & Gottlieb, 2002). Excessive daytime sleepiness is evident when it negatively affects the



patient's daily activities. It is also demonstrated when the Epworth Sleepiness Scale score is greater than 10 (Johns, 1991; Sassani et al., 2004; Talmage, Hudson, Hegmann, & Thiese, 2008).

### **Polysomnogram**

Polysomnogram is an overnight procedure requiring the patient to spend a night in a sleep center. Multichannel electrophysiological recordings of electroencephalogram, electroculogram, electromyogram, and electrocardiogram are used to monitor sleep staging, nasal/oral air flow, respiratory effort, oxygen saturation, snoring, heart rate, and leg movement. The equipment used for the polysomnogram continuously records multiple physiological variables to detect disturbance of breathing during sleep and determine the AHI (apnea-hypopnea index) (Dixon, Schachter, & O'Brien, 2003; Somers et al., 2008). The scoring of these variables is performed by a licensed polysomnographer, and a board certified sleep medicine professional should interpret the study.

### **Continuous Positive Airway Pressure (CPAP)**

CPAP is the most efficacious treatment for OSA. CPAP is a device that maintains positive airway pressure according to pre-set values determined by the polysomnogram titration. It acts as a pneumatic splint for the pharyngeal airway eliminating apneas, hypopneas, and snoring during all stages of sleep (Bazzano, Khan, Reynolds, & He, 2007). It is applied via nasal/face mask (with many choices of facial interface) and tubing connected to the CPAP machine.

## **High-risk Patients**

The pathophysiology of OSA is complex and differs among individuals. In this study, high-risk patients are those displaying a combination of obesity with any of the following diagnoses: hypertension, diabetes mellitus type 2, dyslipidemia, arrhythmias, and coronary artery disease; or non-obese patients displaying a combination of two or more of the above mentioned diagnoses. There are other OSA high-risk characteristics, such as male gender, middle-age, snoring, witnessed apnea or gasping, hypersomnolence, crowded pharyngeal airway (Mallampati classification III or IV) (Jacobs & Coffey, 2009), enlarged neck size, morning headache, and sexual dysfunction (Somers et al., 2008). Further risk factors include abuse of sedatives, alcohol, and tobacco, as well as hereditary factors (Pagel, 2008). However, many of these factors are the focus of current screening measures and the purpose of this study is to determine whether something as simple as particular combinations of diagnoses can be used to identify individuals at risk for OSA. Hence, assessment of these other high risk factors is not included in the present study.

## **High-risk Diagnosis**

For the purpose of this study the high-risk diagnoses are obesity, hypertension, diabetes mellitus type 2, dyslipidemia, arrhythmias, and coronary artery disease. These diagnoses were chosen due to their frequent incidence in a PHC setting and the frequent co-occurrences among these diagnoses observed in the patients who were positive for OSA in the principal investigator's (PI) PHC practice. Furthermore, the literature is prolific in linking these diagnoses with OSA. For instance, untreated OSA contributes to persistent high blood pressure as it does not allow the expected decrease in blood pressure at night (Devulapally et al., 2009; Endeshaw,

White, Kutner, Ouslander, & Bliwise, 2009; Golbin, Somers, & Caples, 2008); about 50% of individuals with OSA are hypertensive (Devulapally et al., 2009; Somers et al., 2008). However, there is a gap in the literature linking these different combinations of diagnoses with OSA.

## **Obesity**

Obesity is documented as the most important cause of OSA (Hiestand, Britz, Goldman, & Phillips, 2006; Somers et al., 2008). Individuals are considered obese when their body mass index (BMI) is greater than or equal to  $30 \text{ kg/m}^2$ . The BMI is a calculation of an individual's weight and height, and it provides a reliable indicator of body fatness for most people. It does not measure body fat directly, but research has shown that BMI correlates to direct measures of body fat (Centers for Disease Control and Prevention, 2010). It is an inexpensive and easy-to-perform method of screening for weight deviations. The BMI is calculated by dividing weight in kilograms by the square of height in meters. Alternatively, BMI may be calculated by dividing weight in pounds by the square of height in inches and multiplying by a conversion factor of 703 (CDC). For this study, obesity diagnosis will be defined as the documented BMI of  $30 \text{ kg/m}^2$  and above.

## **Primary Health Care**

A primary health care (PHC) practice is an office or clinic setting caring for patients with acute and chronic illnesses. It also provides preventive care and health education for all ages and genders (Nutbeam, 1998). Primary care practice, primary health care, general practice, family practice, and internal medicine have many common functions, which are all classified under the PHC category for this study.

## **Primary Care Practitioner**

Primary care practitioners (PCPs) are professionals practicing in primary health care. They might be referred to as clinicians, healthcare practitioners, healthcare providers, primary care providers, or family care practitioners. They are licensed professionals who deliver health care in a systematic and professional way for common medical problems. They may be a physician, a physician assistant, or a nurse practitioner (Vorvick & Zieve, 2009).

## **Screening Tools**

Screening tools are instruments designed to help in the identification of a specific disorder or multiple areas of concern. They do not intend to be conclusive for diagnostic purpose, but rather indicate need of further assessment. The sensitivity of screening tools is the probability they will identify the positive patients and their specificity is the probability they will correctly identify the negative patient. Screening tools aid in the examination of usually asymptomatic individuals to detect those with a high probability of having or developing a given disease (Somers et al., 2008). Key OSA screening tools will be further described in chapter 2.

## **Assumptions**

The reliability of the findings of this study depends on the following underlying assumptions: (1) sleep centers where this study is conducted have a sample population representative of the local community; (2) the technicians and clinicians in the sleep centers have practice behaviors representative of standard care; and (3) the data are accurate in the health records (as disclosed by the patient and/or referring clinician, and as entered by the sleep center

technicians and/or clinicians). These assumptions are appropriate given the available data and settings.

### **Implications for Practice**

The proper screening of high-risk patients leading to diagnosis and treatment of OSA has at least three implications for practice. First, proper screening has the potential to improve patient outcomes ranging from improved health conditions to better quality of life when newly diagnosed patients receive appropriate treatment (Somers et al., 2008). Second, more appropriate treatment also has the benefit of health care savings. Third, PCPs' time may be saved for other assessment and health teaching if study findings support the use of particular diagnoses for detecting an increased risk for OSA. Results of this study could be combined with medical information system programming to create an electronic warning message that appears when particular combinations of diagnoses are present and there is no evidence of a polysomnogram being ordered.

At the very least, knowledge gained from this study is expected to add to the present literature and fill the gap regarding the importance of common combinations of diagnoses found in a PHC setting to the risk of OSA. The results of this study will be disseminated in several forms, such as professional publications, presentations at professional conventions, and local seminars. It is anticipated that this study will present significant evidence-based data to impact PCPs' practice in the proper screening for OSA.

## Summary

The need to find alternative ways for proper screening of OSA high-risk patients is evident from the continuous under-diagnosing of OSA. PCPs are positioned in a key place to improve the number of patients diagnosed and treated for OSA as they treat patients for other common diagnoses that could be related to OSA. This study has the potential to demonstrate how the different combinations of common diagnoses, such as obesity, hypertension, diabetes mellitus type 2, dyslipidemia, arrhythmia, and coronary artery disease, can be used by PCPs to predict patient's risk for OSA. One main value of these diagnoses combinations is how fast and easy it is for PCPs to visualize them and identify OSA high-risk patients. Also, this information could be used to create an electronic alert to cue PCPs to order a polysomnogram.

The next chapters present an in-depth development of this study. In chapter two, the literature relevant to the research question is reviewed. There is prolific research on the topic of OSA and its correlation with common diagnoses seen in a PHC, but there is a gap in the literature that describes the use of combinations of these diagnoses as predictors for high risk patients likely to be diagnosed with OSA. Next, chapter three presents the study design, methods, and the data analysis method. Ethical considerations including security of protected health information and limitations of the study are discussed as well. In chapter four, the findings are presented objectively according to results of statistical analysis. Finally, chapter five focuses on a discussion of the findings supporting the answer to the research question. Potential confounding variables and the effect of study limitations on conclusions is discussed. Implications for practice and recommendations for further studies will also be presented.

## CHAPTER 2: LITERATURE REVIEW

This chapter will provide a thorough discussion of the current literature regarding obstructive sleep apnea (OSA). It is divided into six sections. First, an overview of what is known about OSA with respect to pathophysiology and epidemiology is presented. Next, risk factors for OSA are reviewed. In the third section, the cost associated with untreated OSA is discussed. The following section presents the literature regarding the treatment of choice for OSA. In the fifth section, the state of the science with respect to OSA screening is reviewed. Finally, a case is made for using specific common diagnoses as an alternative to currently available screening methods.

### Obstructive Sleep Apnea

OSA is a condition featuring several episodes of apnea (complete airway obstruction) and or hypopnea (partial airflow obstruction) despite inspiratory efforts. These events usually cause arousals and sleep fragmentation. The recurrent events of airway obstruction often result in oxygen desaturation and subsequent increase in arterial carbon dioxide (American Academy of Sleep Medicine Task Force, 1999). The hypoxia severity may vary according to the number of airway obstruction episodes. It may range from five to hundreds of events per hour (Khayat, Patt, & Hayes, 2009). The diagnosis of OSA is confirmed when the polysomnogram shows apnea-hypopnea index (AHI) or respiratory disturbance index (RDI) of five or more and the patient presents daytime sleepiness, fatigue, sleep disturbance, waking up gasping for air, or loud snoring. Also, in the absence of symptoms, the diagnosis of OSA is granted when AHI or RDI is equal or greater than 15 (Epstein et al., 2009). The severity levels of OSA are related to the AHI

or RDI score: 5-14 mild, 15-29 moderate, 30 or more severe (American Academy of Sleep Medicine Task Force, 1999; Epstein et al., 2009; Young et al., 2002).

## **Pathophysiology**

The pathophysiology of OSA is multi-factorial and not well-understood. The potential mechanism is related to reduced oxygenation caused by the repeated apneas and hypopneas events. Therefore, surges of the sympathetic activation, including rises of catecholamine levels, leads to endothelial dysfunction (Eckert & Malhotra, 2008). Moreover, there is evidence showing increased inflammatory markers such as C-reactive protein in patients diagnosed with OSA (Golbin et al., 2008; Khayat et al., 2009; Valham et al., 2008). The upper airway anatomy in patients diagnosed with OSA is usually smaller and narrower than patients without this condition. This presentation of the soft tissue structures surrounding the upper airway promotes its collapse (Schwab et al., 1995). The Mallampati classification scores the visibility of the tonsils, uvula, and soft palate. The visibility of these structures is scored from one (complete visualization) through four (no visualization) (Jacobs & Coffey, 2009). The upper airway has multiple purposes, including passage of air, food, and liquids. To accomplish these tasks effectively, the muscle structures have collapsible properties allowing intermittent closure during breathing, swallowing, and speech. Unfortunately, these mechanisms may fail during sleep and collapse, blocking the air passage (Eckert & Malhotra, 2008). The recurrent blockage of air during sleep decreases the oxygen saturation (hypoxemia) and increases the concentration of carbon dioxide in the blood (hypercapnia) leading to sympathetic activation. These blockages can be complete (apnea) or partial (hypopnea) and may cause arousal and sleep fragmentation (Eckert & Malhotra, 2008).



## **Epidemiology**

An analysis of the Sleep in America 2005 Poll of the National Sleep Foundation showed that about 25% of the adult population is at risk for OSA (Hiestand et al., 2006). OSA is the most common of the sleep disorders (Calvin & Somers, 2009) with estimates of 2% to 7% of the adult population worldwide (Punjabi, 2008). There is consensus that the prevalence of OSA in a PHC setting is higher than in the general population (N. C. Netzer et al., 2003). This may be explained by common diagnoses seen in PHC that are directly associated with OSA. For instance, studies indicate that there is strong evidence linking OSA with cardiovascular diseases (Khayat et al., 2009; N. C. Netzer, Stoohs, C. M. Netzer, Clark, & Strohl, 1999; Somers et al., 2008).

The Busselton Health Study demonstrated, after a 14-year follow-up, that moderate and severe OSA is an independent risk factor for all-cause mortality associated with 33% mortality versus 6.5% of healthy participants (Marshall et al., 2008). The Wisconsin Sleep Cohort found significant mortality risk associated with untreated severe OSA in its 18-year follow-up study. Severe OSA was an independent factor for all-cause mortality with three-fold greater risk compared with the population without OSA (Young et al., 2008). Considering the high mortality risk of severe OSA, treatment is recommended even for those patients without symptoms of sleepiness (Pack et al., 2008). Patients identified as high-risk for OSA should be follow-upped with a polysomnogram. Studies have shown that about 70% of high-risk individuals screened with polysomnogram receive a diagnosis of OSA (Sassani et al., 2004).

## **Risk Factors for OSA**

### **Age and Gender**

Age has been indicated as a risk factor for OSA, but there is no clear consensus among several studies as to the age range at risk. Many studies present middle-age as high-risk, but the definition of middle-age can vary considerably among authors, with the lower range varying from 40 to 55 years. However, there is consensus that OSA incidence increases with age and plateaus about age 65 (Eckert & Malhotra, 2008; Hiestand et al., 2006; Pavlova, Duffy, & Shea, 2008; Punjabi, 2008). The deterioration of the upper airway reflexes and anatomic changes due to the aging process may place older people at high-risk for OSA (Eckert & Malhotra, 2008).

Middle-age and male gender have been associated with increased risk for OSA (Gurubhagavatula et al., 2008; Pagel, 2008). In a 7-year follow-up study with middle-aged healthy men, OSA was associated with increased risk to develop cardiovascular diseases in almost five-fold. In the same study, when OSA was not treated the cardiovascular mortality risk increased close to eleven-fold (Peker, Hedner, Norum, Kraiczi, & Carlson, 2002). In a study comprising men with mean age 47 years, there was indication of cognitive dysfunction related to OSA (Saunamäki, Himanen, Polo, & Jehkonen, 2009). It is not completely understood why OSA prevalence is higher in males. The closest explanation is related to the fat deposition around the pharyngeal airway which is more increased in males than in females (Eckert & Malhotra, 2008). Males also have increased length of the pharyngeal airway which has been linked to airway propensity to collapse.

## **Metabolic Syndrome**

Metabolic syndrome is characterized by a combination of disorders, such as obesity, diabetes mellitus type 2, dyslipidemia, and hypertension. Incidentally, these diseases have been independently correlated with OSA. Obesity contributes to OSA not only by its anatomic effect, but also by its dysfunctional metabolic activity (Cuhadarođlu, Utkusavař, Oztürk, Salman, & Ece, 2009). In obese patients, OSA predicts the severity of insulin resistance due to the hypoxia insult (Polotsky et al., 2009). Moreover, sleep deprivation is a common consequence of sleep fragmentation due to OSA, which has been associated with metabolic syndrome and more specifically to insulin resistance and high levels of glucose (Calvin & Somers, 2009).

## **Obesity**

Obesity is defined as Body Mass Index (BMI) equal or over 30 kg/m<sup>2</sup>; overweight is considered BMI equal or over 25 kg/m<sup>2</sup>. BMI is the calculation of an individual's weight and height. The prevalence of obesity in the United States (US) has been steadily increasing at alarming rates in the last few years; estimates are that more than half of the US population is overweight (Center for Disease Control and Prevention (CDC). Division of Nutrition, Physical Activity and Obesity, National Center for Chronic Disease Prevention and Health Promotion, 2010). It is well-documented in the literature that there is a direct relationship between obesity and OSA (Dixon et al., 2003; Hiestand et al., 2006; Polotsky et al., 2009; A. R. Schwartz et al., 2008; Tasali & Ip, 2008; Wolk et al., 2003). Obese patients present several features associated with OSA; the most significant in predicting OSA severity was neck circumference equal or greater than 43 cm (17 inches) for both men and women (Dixon et al., 2003). In a study with patients presenting for bariatric surgery, the BMI was directly related to OSA incidence and

severity. For patients with BMI between 40 and 50 kg/m<sup>2</sup> the OSA incidence was close to 74%, and those with BMI greater than 60 kg/m<sup>2</sup> the OSA incidence increased to nearly 95% (Lopez et al., 2008). Obesity is a significant risk factor in the progression of OSA (A. R. Schwartz et al., 2008).

## **Diabetes Mellitus Type 2**

Diabetes mellitus type 2 has been associated with OSA in several studies worldwide (Aronsohn, Whitmore, Van Cauter, & Tasali, 2010; Botros et al., 2009; Lam et al., 2010; Tasali & Ip, 2008). Sleep fragmentation and hypoxia are common occurrences in OSA which may cause insulin resistance and adversely affect glucose metabolism (Polotsky et al., 2009; Tasali & Ip, 2008). Patients with diabetes and untreated OSA have demonstrated poor glucose control which is adversely affected by the OSA severity (Aronsohn et al., 2010). In a 5-year observational cohort study with 544 participants, OSA was found to independently increase the risk of developing diabetes. Furthermore, this study suggested that regular use of CPAP may decrease the risk of diabetes in patients with severe OSA (Botros et al., 2009).

## **Dyslipidemia**

Dyslipidemia has been linked to OSA in several cross-sectional studies (Drager, Jun, & Polotsky, 2010; L. Lavie, 2008). Even though the independent association of the OSA effect on dyslipidemia is still debatable, significant improvement on lipid profile has been reported on OSA patients treat with CPAP (Cuhadaroğlu et al., 2009). The inflammatory and immune response activated by the hypoxia experienced in OSA may cause endothelial cell dysfunction promoting dyslipidemia (L. Lavie, 2008).

## Hypertension

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) places OSA as significant cause of secondary hypertension (US Department of Health and Human Services. National Institute of Health. National Heart, Lung, and Blood Institute Committee, 2003). Hypertension has been linked to OSA in several studies (Bazzano et al., 2007; Calvin & Somers, 2009; Devulapally et al., 2009; Dodson, 2008; Endeshaw et al., 2009; Golbin et al., 2008; Khayat et al., 2009; Merritt, 2004; Peker et al., 2002; Somers et al., 2008; US Department of Health and Human Services. National Institute of Health. National Heart, Lung, and Blood Institute Committee, 2003; Wolk et al., 2003). The peripheral vasoconstriction caused by the repetitive hypoxia during respiratory events interferes with the homeostasis balance affecting blood pressure control (Golbin et al., 2008). Hypoxemia stimulates the release of catecholamine which involves vasoconstrictor hormones such as norepinephrine, epinephrine, and dopamine (Eckert & Malhotra, 2008). The intermittent state of nocturnal hypoxemia triggers the sympathetic system causing surges in the blood pressure, which persist during the day in a carryover effect (Khayat et al., 2009). Nocturnal blood pressure in normal individuals presents the dipping phenomenon where it decreases 10-15% compared to their awake levels. However, OSA does not allow the expected decrease in blood pressure at night and contributes to persistent high blood pressure during the day as well (Devulapally et al., 2009; Endeshaw et al., 2009; Golbin et al., 2008). Kapur (2008) and colleagues did a cross-sectional analysis including all subjects of the Sleep Heart Health Study (1996), and they found stronger association of hypertension with OSA in individuals with daytime sleepiness compared with individuals not reporting sleepiness. Additionally, OSA has

been linked to aggravation of hypertension related to obesity due to common pathophysiological mechanisms of OSA and obesity (Wolk et al., 2003).

### **Cardiovascular Diseases**

Besides hypertension, many of the cardiovascular diseases have been linked to OSA. The Sleep Heart Health Study had 6,046 participants in a multi-center cohort study. It was conducted by the National Heart, Lung, and Blood Institute, and it demonstrated the relationship of breathing sleep disorders with cardiovascular diseases among other implications (Sleep Heart Health Study Research Group, 1996). Increasing evidence argues for an association between OSA and cardiac arrhythmias, including atrial fibrillation, and bradyarrhythmias (Devulapally et al., 2009; Golbin et al., 2008). In a 10-year study with patients diagnosed with coronary artery disease, OSA was considered an independent risk factor for stroke events. Patients with mild and severe OSA presented 2.4 and 3.6 times increased risk for strokes respectively (Valham et al., 2008).

### **The Costs of Untreated OSA**

Besides the significant direct health care costs associated with untreated OSA and the aggravation of many diseases, other costs include motor vehicle accidents and lost productivity. Daytime hypersomnolence is caused by sleep fragmentation which is one of the hallmarks of OSA. The implications of daytime sleepiness for commercial drivers in particular are severe and costly (Gurubhagavatula et al., 2008). In a controlled study with 1,443 truck drivers 13% were found to be high-risk for OSA and 94.8% of those had a polysomnogram positive for OSA (Talmage et al., 2008). Significant visual vigilance decline was found in drivers with untreated

OSA (Tippin, Sparks, & Rizzo, 2009). Gurubhagavatula's study estimates cost of motor vehicle accidents due to drivers with untreated OSA at 2.4 billion dollars per year. Another study by Sassani (2004) estimates cost of OSA-related collisions, including fatalities, at 15.9 billion dollars in the year 2000. Furthermore, the same study estimated that treating drivers for OSA could have saved 980 lives involved in those crashes.

Work productivity has been estimated to be decreased in 37% due to sluggish thought process and neurocognitive impairment of untreated employees with OSA (AlGhanim et al., 2008; Gurubhagavatula et al., 2008). Decreased work performance may be related to daytime hypersomnolence, irritability, reduced vitality, besides cognitive dysfunction (Pagel, 2008). Screening high-risk employees, diagnosing, and treating them with CPAP has shown significant economic benefit (AlGhanim et al., 2008).

### **Treatment for OSA**

Continuous positive airway pressure (CPAP) is the treatment of choice for OSA (Bazzano et al., 2007). When the diagnosis of OSA is confirmed with a polysomnogram, these patients are referred for a second-night polysomnogram titration to assess appropriate pressure settings for the CPAP. There are a few other treatment options for OSA, but discussing them all is beyond the scope of this study. Patients properly treated with CPAP often have a total resolution or significant improvement of respiratory events. Among other benefits, patients with moderate to severe OSA have demonstrated improvement in the beta cell insulin secretory capacity (Calvin & Somers, 2009). Moreover, CPAP use for at least 4 hours per night promotes significant control in glucose homeostasis (Calvin & Somers). Studies also have shown that patients treated with CPAP have significant reduction in total cholesterol, low-density

lipoprotein, and leptin levels (which has been linked to insulin sensitivity and resistance) (Cuhadaroglu et al., 2009).

Patients treated for OSA with CPAP have decreased C-reactive protein (CRP) levels (Khayat et al., 2009). CRP is a significant risk factor for cardiovascular diseases (Khayat et al., 2009) and it has been connected with OSA in several studies. Furthermore, the effect of CPAP in reducing blood pressure levels has been demonstrated by several studies (Bazzano et al., 2007; Devulapally et al., 2009). The most significant benefit of proper CPAP treatment on blood pressure control was noted in patients with severe OSA and severe hypertension (Devulapally et al., 2009).

CPAP treatment has demonstrated benefit in decreasing depression symptoms for patients with concomitant diagnosis of OSA (D. J. Schwartz & Karatinos, 2007). There is a high incidence of depression associated with OSA, and it has been suggested that it is due to the effect of intermittent hypoxia on neural alterations (Cross et al., 2008). Moreover, OSA has been known to act as a physiological trigger for headaches including migraine, cluster, tension-type, and others as they may be precipitated by disturbance of the sleep pattern. Morning headaches in particular have been associated with OSA which are resolved after effective treatment with CPAP (Rains & Poceta, 2006).

### **Screening for OSA**

Primary care practitioners (PCPs) play an important role in identifying patients at high-risk for OSA. They are in a key position to recognize comorbidities and physical features associated with OSA (Pagel, 2008). They also have the opportunity to identify patients not presenting with the classic symptoms but with enough evidence of comorbidities suggestive of



high risk for OSA (S. A. Chung et al., 2002; Culpepper & Roth, 2009; Doghramji, 2008; Khassawneh et al., 2009; P. Lavie, 2006). However, several studies have demonstrated that PCPs recognize less than 15% of patients identified with OSA (N. C. Netzer et al., 1999; Reuveni et al., 2004; Skjodt, 2008). For instance, the Berlin questionnaire was validated for use in primary health care settings since 1996 (N. C. Netzer et al., 1999) but there is no significant evidence showing its wide use by PCPs (McNicholas, 2008), hence the low percentage of patients screened by PCPs over a decade later. In Jordan, a cross-sectional survey was conducted in five PHC centers and the results showed that OSA symptoms were frequently present but often not recognized (Khassawneh et al., 2009). PCPs using screening tools or with adequate training to take an accurate sleep history have substantially improved identification of OSA high-risk patients (Khassawneh et al., 2009; P. Lavie, 2006; N. C. Netzer et al., 1999; Skjodt, 2008).

Well-informed PCPs can give significant support for patients treated for OSA. They can ensure patients receive adequate information and follow-up when treated with CPAP. PCPs provide significant support by checking patients for persistence, improvement or resolution of symptoms such as snoring and daytime somnolence after using CPAP (Doghramji, 2008). Initially, and after the adjustment phase, PCPs continue to be an integral part of the long-term follow-up, checking for adherence to treatment, comfort in using the equipment, knowledge of equipment maintenance, and reassessment of weight increase or decrease over their baseline (Culpepper & Roth, 2009; P. Lavie, 2006; Merritt, 2004).

Screening tools have been developed to help PCPs to identify the high-risk patients for OSA, but, no single tool used alone has sufficient sensitivity and specificity to diagnose OSA or predict its severity (Jacobs & Coffey, 2009). Screening tools may function as a reminder to PCPs to ask patients about their sleep histories and identify the patients at risk for OSA (Reuveni et al.,

2004). Some methods utilize self-reported questionnaires where patients rate their own sleepiness and risk factors.

### **Epworth Sleepiness Scale**

The Epworth Sleepiness Scale (ESS) was created in 1991 and revised in 1997 by Dr. Murray Johns who is an internal medicine physician with specialization in sleep medicine in Australia. The ESS has been translated and used by experts in sleep medicine in many countries around the world (Johns, 2009; Rosenthal & Dolan, 2008). ESS has been validated in many languages including Spanish (Chica-Urzola, Escobar-Córdoba, & Eslava-Schmalbach, 2007; Vidal et al., 2007), Chinese (Chiner, Arriero, Signes-Costa, Marco, & Fuentes, 1999), Japanese (Takegami et al., 2009), and Portuguese (Bertolazi et al., 2009).

The ESS was created with the purpose of measuring excessive daytime sleepiness in adults. It is a simple self-administered 8 item questionnaire of 8 specific common situations in daily living. These questions were developed based on identified low stimulus activities promoting sleepiness. Individuals are requested to rate on a scale 0-3 how likely they would be to doze off or fall asleep in each situation described in the 8 questions. The scale ranges from: (0) would never doze, (1) slightly chance of dozing, (2) moderate chance of dozing, (3) high chance of dozing. The eight situations are: (I) sitting and reading, (II) watching television, (III) sitting, inactive in a public place, (IV) as a passenger in a car for an hour without a break, (V) lying down to rest in the afternoon when circumstances permit, (VI) sitting talking to someone, (VII) sitting quietly after lunch without alcohol, and (VIII) in a car, while stopped for a few minutes in the traffic. Out of the total possible score of 24 points, 10 or higher is considered abnormal (Johns, 1991). The scoring is simple and may take just a few seconds.

The ESS was tested for reliability and internal consistency in a study with 104 medical students and 150 patients. It was retested after five months with no significant change for the healthy students and with significant change for the patients treated for OSA. The paired ESS scores were consistent and highly correlated ( $r=0.82$ ) with the Cronbach's alpha (0.88) (Johns, 1992). Rosenthal (2008) discussed the low sensitivity (66%) of the ESS in identifying OSA at score of 10 and also the low specificity of only 48%. One limitation of the ESS is related to patients reporting daytime sleepiness which may be due to other conditions including a fast-paced life style (Rosenthal & Dolan, 2008). On the other hand, patients may under-report daytime sleepiness. For instance, patients may gradually and chronically become hyper-somnolent during the day and not realize it (Dodson, 2008).

### **Berlin Questionnaire**

The Berlin Questionnaire was created at the Conference on Sleep in Primary Care in April 1996 in Berlin, Germany. This conference had representation of 120 American and German pulmonary and primary care physicians. The Berlin Questionnaire was developed based on studies across the literature. They selected questions to elicit factors or behaviors that consistently predicted the presence of sleep apnea (N. C. Netzer et al., 1999).

The questions on the Berlin Questionnaire focus on risk factors for sleep apnea. It consists of one introductory question and four follow-up questions concern snoring; three questions addressing daytime sleepiness, with a sub-question about sleepiness while driving. One question concerns history of high blood pressure. Patients are also asked to provide information on age, weight, height, gender, neck circumference, and ethnicity. The body mass index is calculated from self-reported weight and height (N. C. Netzer et al., 1999).

The predictive values for the Berlin Questionnaire vary among different populations. In a primary care setting the sensitivity ranges from 54% to 86% and the specificity from 43% to 87%. The reliability according to the agreement and Cohen coefficient of test-retest was 96.3%. However, the sensitivity and specificity were much lower (below 70%) and less predictive of OSA in patients referred to sleep centers and in patients undergoing pulmonary rehabilitation (F. Chung et al., 2008b).

### **STOP-BANG Questionnaire**

Dr. Frances Chung and his team of seven researchers in Canada developed and validated the STOP-BANG questionnaire in 2008 for OSA screening in the surgical setting. They were looking for a concise and easy screening tool to use for pre-anesthesia evaluation of patients at risk for OSA. By recognizing high-risk patients undiagnosed for OSA, it was expected that perioperative morbidity and mortality would be decreased (F. Chung et al., 2008a; F. Chung et al., 2008b; Lopez et al., 2008; Skjodt, 2008).

The four questions of the STOP questionnaire were based on the Berlin questionnaire related to (S) snoring, (T) tiredness, (O) observed obstruction (stopped breathing), (P) pressure (hypertension). The observed characteristics of individuals at high-risk for OSA from the STOP questionnaire pilot study led to the addition of the BANG questions. (B) Body Mass Index (BMI) greater than 35 kg/m<sup>2</sup>, (A) age over 50 years, (N) neck circumference greater than 40 cm (16 inches), and (G) male gender. The STOP-BANG questionnaire with three or more yes responses suggests high risk for OSA (F. Chung et al., 2008a).

A pilot study was conducted with 592 preoperative adult patients. They answered the STOP questionnaire and underwent an overnight polysomnogram regardless of the score. After

the pilot study the same research process was conducted for 1,875 patients and the “BANG” questions were added to the STOP questionnaire. The results from the polysomnogram were analyzed considering the predictive parameters of the STOP-BANG questionnaire to evaluate its validity. The polysomnogram with apnea-hypopnea index (AHI) over 5 was positive for the diagnosis of OSA. The STOP-BANG questionnaire sensitivity at AHI above 5 (mild OSA) was 83.6% and the specificity was 56.4%; at AHI 15 and above (moderate OSA) the sensitivity was 92% and the specificity was 43%; at AHI 30 and above (severe OSA) the sensitivity was 100% and the specificity was 37% (F. Chung et al., 2008a).

### **Summary**

The literature is rich with evidence linking obstructive sleep apnea (OSA) to several debilitating chronic diseases such as obesity, hypertension, diabetes mellitus type 2, and cardiovascular diseases. However, research evaluating the use of combinations of these high-risk diagnoses for identifying patients at risk for OSA was not found in the literature. Despite well-established evidence showing severe adverse effects for patients with untreated OSA, this disorder continues to be under-diagnosed. Proper screening and treatment for OSA has been linked to improved patients’ outcomes ranging from improved health conditions to better quality of life. As documented in multiple studies, PCPs are in a key position to identify high-risk patients for OSA, but frequently these patients are unrecognized. A few screening tools are available for screening of patients at risk for OSA, but they are not widely used in the PHC setting; time constraints often keep PCPs from focusing on OSA screening. It is evident that there is a need to offer alternative ways for PCPs to properly screen patients at risk for OSA.

This study has the potential to demonstrate how the different combinations of common diagnoses such as obesity, hypertension, diabetes mellitus type 2, dyslipidemia, arrhythmia, and coronary artery disease can be used by PCPs to predict a patient's risk for OSA. The use of diagnoses combinations may be a fast and simple way for PCPs to identify the patients at risk for OSA because they see patients with these common diagnoses on a daily basis. OSA screening could be made even easier when using electronic health records. An electronic alert based on the diagnoses combination algorithm could prompt PCPs to order a polysomnogram. This study may lead PCPs to increase the screening of high-risk patients, and ultimately reduce the under-diagnosis of OSA.

## CHAPTER 3: STUDY OVERVIEW

The research question this study addressed was: What is the effect of obesity in combination with one as compared to two or more other high-risk diagnoses on the likelihood of being diagnosed with obstructive sleep apnea in a primary health care setting? Obstructive sleep apnea (OSA) high-risk diagnoses in this study are defined as obesity, hypertension, diabetes mellitus type 2, dyslipidemia, arrhythmias, and coronary artery disease. This chapter presents the study methods, including setting and design and rationale for their appropriateness to answer the research question; method for selecting study participants and data collection; protection of human subjects and ethical considerations; and data analysis to evaluate study outcomes. The limitations of this study are also presented, along with a discussion of implication for practice.

### Setting

The setting of this study was six sleep centers located in five cities in Central Florida that are under the administration of Florida Hospital Sleep Centers. They are certified by the American Academy of Sleep Medicine or The Joint Commission. Most of these sleep centers operate seven days a week and have a high volume of patients diagnosed with OSA. Hundreds of different practitioners refer a variety of patients, resulting in an average of 3000 polysomnograms per year among the six centers. These patients are diverse in their ethnicity, race, gender, and socioeconomic status. They represent a mix of health insurance coverage including Medicare, Medicaid, private insurance, Health Maintenance Organization, and self-pay.

## Design

This study was a descriptive, cross-sectional study that used a two by two design (see Table 1).

Table 1: Two by Two Design

	<b>Obesity: Yes</b>	<b>Obesity: No</b>
One non-obesity high-risk diagnosis	Expect high OSA	Expect low OSA
Two or more non-obesity high-risk diagnoses	Expect highest OSA	Expect high OSA

## Sample

A random sample size of 220 electronic health records was selected from a pool of available records. These patients completed a polysomnogram for assessment of OSA from January 2009 to December 2010 in the previously mentioned sleep centers. The following were the health record inclusion criteria: (a) polysomnogram ordered by PCPs (b) patient age 18 and above. The exclusion criteria were: (a) polysomnogram done for titration, re-titration, or reevaluation of previously diagnosed OSA; (b) polysomnogram done for evaluation of sleep disorders other than OSA. The data necessary for this study were available via retrospective chart review. Therefore no contact was made with patients.

The total sample had 49% (108) of males and 51% (112) of females. The age range was from 18 to 82 years of age and the mean age was 48.9. The sample had a BMI range of 19 to 55 kg/m<sup>2</sup> with a mean of 32.2 kg/m<sup>2</sup>. The total sample had 58% (127) of patients with obesity, 46% (102) patients with hypertension, 20% (43) of patients with Diabetes Mellitus type 2, and 37%



(81) of patients with dyslipidemia. Out of the patients diagnosed with OSA, 63% of them had either moderate or severe OSA (see Table 2).

Table 2: Sample Demographics

	<b>Total Sample (N=220)</b>	<b>OSA Positive Sample Subgroup (n=154)</b>
<b>Gender</b>		
Male	49% (108)	61% (94)
Female	51% (112)	39% (60)
<b>Age</b>		
Mean	48.9	50.7
(Standard Deviation)	(13.0)	(13.6)
Median	49	51
(Range)	(18-82)	(18-82)
<b>BMI</b>		
Mean	32.2	33.6
(Standard Deviation)	(7.5)	(7.5)
Median	30	32
(Range)	(19-55)	(19-55)
<b>Diagnoses</b>		
Obesity	58% (127)	69% (106)
HTN	46% (102)	56% (86)
DM	20% (43)	27% (41)
Dyslipidemia	37% (81)	45% (69)
Arrhythmia	6% (14)	6% (10)
CAD	7% (16)	9% (14)
<b>AHI/RDI</b>		
Mild (5 to 14.9)	-	37% (57)
Moderate (15 to 29.9)	-	29% (44)
Severe (30 and above)	-	34% (53)

The sample size ( $n=220$ ) was sufficient for estimating a logistic regression model with two independent variables plus the interaction term, making three predictors. There were no missing data because only records that had full data available were used. Given that the

incidence of OSA in the patient group for which health records were available was 70%, and 58% of the sample were obese, the power in the logistic regression for detecting an odds ratio of 2.0 or bigger was 80%, assuming significance level of  $p < 0.05$ .

### **Procedure**

The principal investigator (PI) applied for Institutional Review Board (IRB) approval from the University of Central Florida first. Right after this approval was received, the PI applied for Florida Hospital IRB approval which allowed access to the data at the sleep centers. The review of health records was initiated immediately after the approval from both institutions' IRB was received. The PI recorded data for the study variables using electronic data collection after selecting health records that met the inclusion and exclusion criteria. The chart review was done using electronic health records of the sleep centers. The study timeline was as follows: (a) data collection February 2011; (b) data analysis February and March 2011; (c) summary of study results and conclusion March 2011.

### **Study Variables**

The demographic variables used to describe the sample were age and gender. The dependent variable is a diagnosis of OSA which is a dichotomous variable. A value of (1) was assigned for OSA positive and a value of (0) was assigned for OSA negative. OSA is considered positive when the apnea-hypopnea index (AHI) or respiratory disturbance index (RDI) is equal or greater than five. The variables composing the independent variables are obesity, hypertension, diabetes mellitus type 2, dyslipidemia, arrhythmia, and coronary artery disease. They were divided into obesity and non-obesity high-risk diagnoses. The body mass index (BMI)

was collected and used to create the obesity variable. A value of (1) was assigned if the BMI was greater than or equal to 30 kg/m<sup>2</sup> and a value of (0) was assigned if the BMI was less than 30 kg/m<sup>2</sup>. The non-obesity high-risk diagnoses variables were created by assigning a value of (1) for the presence of and a value of (0) for the absence of hypertension, diabetes mellitus type 2, dyslipidemia, arrhythmias, or coronary artery disease.

### Data Analysis

Descriptive statistics (mean, standard deviation, range, frequency, percentage) were used to describe the sample (gender and age, and BMI) and summarize key study variables (obesity, hypertension, diabetes mellitus type 2, dyslipidemia, arrhythmias, and coronary artery disease). Logistic regression was used to address the research question. For this analysis, the dependent and independent variables are nominal and they were coded as follows: dependent variable – obstructive sleep apnea: yes (1), no (0); independent variables – obesity: yes (1), no (0) and non-obesity high-risk diagnosis 1 (0), non-obesity high-risk diagnosis 2+ (1). For analysis purposes the interaction term was the result of obesity multiplied by non-obesity high-risk diagnoses categories. Therefore, the logistic regression model contained the two main effect variables (independent variables) and one interaction variable. The software system used for the data analysis was SPSS 17.0.

If the interaction effect was significant, a post-hoc analysis would be conducted using 3 separate logistic regression analyses as follows: (1) obesity plus one high-risk diagnosis *versus* obesity plus two or more high-risk diagnoses and non-obesity plus two or more high-risk diagnosis; (2) obesity plus two or more high-risk diagnoses *versus* obesity plus one high-risk diagnosis and non-obesity plus two or more high-risk diagnosis; (3) non-obesity plus two or

more high-risk diagnosis *versus* obesity plus one high-risk diagnosis and obesity plus two or more high-risk diagnoses. The odds ratios (ORs) would be evaluated for statistical significance and then compared to determine which combination is most predictive of OSA.

### **Ethical Considerations**

The method of retrospective chart review did not imply significant risks to patients. Their health record numbers were disconnected from the data collected and there was minimal or no risk of identification of patients' records. Data analysis only proceeded with a de-identified data set. The data analysis and final report were at the group level preventing identification of any individuals. Thus, no consent was obtained from patients.

A "study number" was assigned for each health record. The data collected for review was stored in a secure database at Florida Hospital Neuroscience Clinical Research Institute. The file containing the health record number and the study number was also kept by Florida Hospital as per their IRB requirement for data integrity. This information is not available for outside access. It will only be revealed on a need to know basis as required by law.

The PI has active privileges as a healthcare provider at Florida Hospital where this study was conducted. The access to these records was granted by this organization's IRB preparatory research approval as per HIPAA Reviews Preparatory to Research Form and finally by their IRB. The data collection started after the official IRB approvals were received from University of Central Florida and Florida Hospital.

### **Study Limitations**

The main limitation of this study may be related to the sample size. Data are not available from past research to use in estimating the effect size. However, a clinically meaningful effect size was used in estimating the desired sample size for analysis. Another consideration for limitation is the sample from the Central Florida community only. It is possible that clinical diagnoses could vary in different parts of the country with the “culture” of the healthcare providers assigning them. However, this study is for exploratory purposes. Should significant results be obtained, this study could be replicated in other parts of the United States.

### **Study Innovation**

The overwhelming number of patients with undiagnosed obstructive sleep apnea (OSA) can be related to poor screening in the PHC setting (N. C. Netzer et al., 1999; Reuveni et al., 2004; Skjodt, 2008). The use of screening tools such as the Epworth Sleepiness Scale, STOP-BANG, and the Berlin questionnaire are very helpful in proper identification of high-risk patients. However, many PCPs may not be familiar with these tools or may not find the time to use them, thus contributing to the underdiagnosis of OSA. For example, over 85% of people with OSA are not diagnosed (F. Chung et al., 2008a; Somers et al., 2008).

This study investigates whether obesity in combination with other high-risk diagnoses can be used to predict the risk of a positive diagnosis of OSA. Obesity and the other high-risk diagnoses (hypertension, diabetes mellitus type 2, dyslipidemia, arrhythmias, and coronary artery disease) are common diagnoses encountered in a PHC setting. Therefore, the use of these diagnoses combinations to identify OSA high-risk patients may offer a simple way to prompt PCPs to refer patients for a polysomnogram.

There is a gap in the literature regarding combinations of diagnoses commonly seen in a PHC setting as predictors for OSA high-risk. Findings from this study will contribute to the body of knowledge and will warrant further research to generalize these results. Replication in other populations would support the wide use of these diagnoses combination by PCPs. Also, this would be beneficial in educating future PCPs to screen high-risk patients for OSA.

## CHAPTER 4: RESULTS OF STATISTICAL ANALYSIS

The results of the data analysis are presented objectively in this chapter and the discussions of these findings are addressed in the next chapter. The results in Table 3 show the percentage of obstructive sleep apnea (OSA) diagnosis for each variable in the sample without consideration to interaction effects.

Table 3: OSA and the Sample Variables

	<b>Obesity: Yes</b>	<b>Obesity: No</b>
One non-obesity high-risk diagnosis	18%	10%
Two or more non-obesity high-risk diagnoses	32%	10%

The total sample ( $n=220$ ) had 70% (154) of patients positive for OSA. A third (33%, 72 patients) had two or more of the high-risk diagnoses whereas less than a third (27%, 59 patients) had one of the high-risk diagnoses. Obesity was present in 58% (127) of patients in this sample.

### **Obesity with Two Plus High-Risk Diagnoses**

Both obesity and having two or more high risk diagnoses were significant in the logistic regression analysis ( $p < .001$  and  $p = .02$  respectively). However, the interaction term was not significant ( $p = .60$ ), indicating that the combination of obesity and two or more high risk diagnoses does not improve prediction of those with OSA. Model statistics indicated a good fit for the logistic regression: Hosmer & Lemeshow  $p = 1.0$ ;  $-2LL=227.2$ ; Model  $\chi^2 (3) 41.53$ ,  $p < .001$ . The overall classification rate was 73.6%.

The analysis was re-run to estimate odds ratios (ORs) without the interaction term in the analysis. The OR for obesity was 4.2 ( $p < .001$ ). The OR for two or more high-risk diagnoses was 4.3 ( $p < .001$ ). Model statistics indicated a good fit for the logistic regression: Hosmer & Lemeshow  $p = .87$ ;  $-2LL = 227.5$ ; Model  $\chi^2 (2) 41.25, p < .001$ . There was no decrease in overall classification rate when the interaction term was dropped.

Table 4: Sensitivity and Specificity

	<b>Sensitivity</b>	<b>Specificity</b>	<b>Predictive Value of Positive</b>	<b>Predictive Value of Negative</b>	<b>False Positive Rate</b>	<b>False Negative Rate</b>
Obesity	69%	68%	83%	48%	32%	31%
Two or more high-risk diagnoses	44%	86%	88%	40%	14%	56%

Screening tests statistics based on the use of the two significant predictors (obesity and two or more high-risk diagnoses) are depicted in Table 4. The sensitivity for obesity was higher (69%) than for two or more high-risk diagnoses (44%). However, the specificity for two or more high-risk diagnoses was higher (86%) than for obesity (68%).

### **Obesity with One High-Risk Diagnosis**

Obesity in the logistic regression analysis was significant ( $p < .001$ ). However, having one high risk diagnosis was not significant ( $p = .47$ ). The interaction term was not significant ( $p = .57$ ), indicating that the combination of obesity and one risk diagnosis does not improve prediction of those with OSA. Model statistics indicated a good fit for the logistic regression:



Hosmer & Lemeshow  $p = 1.0$ ;  $-2LL=242.2$ ; Model  $\chi^2 (3) 26.60, p < .001$ . The overall classification rate was 70.5%.

## CHAPTER 5: DISCUSSION OF FINDINGS

This chapter presents a thorough discussion to answer the research question: What is the effect of obesity in combination with one as compared to two or more other high-risk diagnoses on the likelihood of being diagnosed with obstructive sleep apnea in a primary health care setting? The findings presented in the previous chapter argue for the importance of using either obesity or two or more of the high-risk diagnoses (hypertension, diabetes mellitus type 2, arrhythmia, and coronary artery disease) independently to identify individuals at risk for obstructive sleep apnea (OSA) in a primary health care (PHC) setting.

The answer to the research question is that the combination of obesity with high-risk diagnoses (two or more, or just one) was not significant, as determined by the interaction term. However, both obesity and two or more high-risk diagnoses had significant effects on the likelihood of being diagnosed with OSA in a PHC setting. Patients with obesity or with two or more of the high-risk diagnoses were found to have over four-fold likelihood of an OSA diagnosis as seen in Table 5. The use of two or more high-risk diagnoses independently of obesity as a predictor for OSA has not been previously described in the literature. However, in this study it was found to be significant in the logistic regression analysis, thus arguing for the use of two or more high-risk diagnoses for identifying patients at risk for OSA.

Table 5: Odds Ratio for OSA Diagnosis for Key Risk Factors

	<b>Odds Ratio</b>
Obesity	4.2
Two or more high-risk diagnoses	4.3

## Effect of Study Limitations on Conclusions

Nevertheless, the study had four main limitations. First, the pool of health records available included only the records with full documentation. Approximately 10% of the records could not be included because the scanning of the medical history was missing. Second, some of the records may have had diagnoses under estimated as their documentations were dependent on accurate disclosure by the patient or primary care practitioner (PCP). Third, the sample is comprised of patient records only from Central Florida and the records did not provide information on race or ethnicity. However, health records used were from six sleep centers located in five different cities. Furthermore, patient characteristics with respect to obesity (69%) and hypertension (56%) in the study sample are consistent with those reported in the literature (Devulapally et al., 2009; Somers et al., 2008; Wolk et al., 2003). Also, the percentage of OSA (70%) in the total sample is similar to percentages reported in the epidemiologic literature (Sassani et al., 2004). This argues for the generalizability of study findings.

Last, the high predictive value found for two or more high-risk diagnoses (88%) and obesity (83%) in predicting OSA in this study was based on an OSA prevalence of 70% of this sample. In the more general adult population, the incidence of OSA is lower. For example, the incidence of OSA in the adult population according to the Sleep in America 2005 Poll of the National Sleep Foundation analysis was about 25%. Thus, it would be expected that the predictive value would be lower in the more general adult population than what was observed in this study. However, it may be important to consider that the incidence of OSA in a PHC setting is higher than in the general population (N. C. Netzer et al., 2003).

## Implications for Practice

The use of either obesity or two or more high-risk diagnoses for identifying patients at risk for OSA in a PHC setting may impact the number of patients sent for a polysomnogram and thus diagnosed with OSA. The literature relates the overwhelming number of patients with undiagnosed OSA to an inadequate screening in the PHC setting (S. A. Chung et al., 2002; Dodson, 2008; P. Lavie, 2006; Merritt, 2004; Reuveni et al., 2004; Skjodt, 2008). The use of two or more high-risk diagnoses may present a fast and simple option for PCPs not currently using the available screening tools to identify the patients at risk for OSA.

These high-risk diagnoses (hypertension, diabetes mellitus type 2, arrhythmia, and coronary artery disease) are common diagnoses seen on a daily basis in a PHC. Therefore, PCPs may not spend extra time for OSA assessment because they are already assessing the patients for the common diagnoses. Also, the medical information system can easily create an electronic alert based on the high-risk diagnoses algorithm that would prompt PCPs to order a polysomnogram.

The proper screening of high-risk patients leading to diagnosis and treatment of OSA has the potential to improve patients' outcomes not only with respect of their improved health conditions, but also improving their quality of life (Somers et al., 2008). Another aspect related to proper OSA treatment is the benefit of health care savings. Besides the significant direct health care costs associated with untreated OSA and the aggravation of many diseases, other costs include motor vehicle accidents and lost productivity (Gurubhagavatula et al., 2008; Sassani, 2004; Talmage et al., 2008). Work productivity has been estimated to be decreased in 37% due to sluggish thought process and neurocognitive impairment of untreated employees with OSA (AlGhanim et al., 2008; Gurubhagavatula et al., 2008). Screening high-risk

employees, diagnosing, and treating them with CPAP has shown significant economic benefit (AlGhanim et al., 2008).

PCPs are in a key position to recognize patients at risk for OSA. However, several studies have demonstrated that PCPs recognize less than 15% of patients identified with OSA (N. C. Netzer et al., 1999; Reuveni et al., 2004; Skjodt, 2008). The use of obesity and two or more high-risk diagnoses may have a modest sensitivity of 69% and 44% respectively in identifying the true positives for OSA, but it represents a significant advance in the identification of OSA high-risk patients compared with the present screenings (less than 15%). The specificity of 68% for obesity and 86% for two or more high-risk diagnoses in this population is significant in identifying the true negatives for OSA.

The sensitivity and specificity of obesity and two or more high-risk diagnoses compared to other screening tools are close enough to demonstrate their value as predictors for a positive OSA diagnosis as seen in Table 6. Two or more high-risk diagnoses has a modest 44% sensitivity, but considering the simple and easy way to use it in a PHC setting it may represent more patients screened than the highest 84% sensitivity of the STOP-BANG. The sensitivity detects the percentage of positive OSA identified by the predictor. However, the predictor is only as good as much as it is used. For instance, the current percentage of PCPs using any screening tool to identify the high-risk patients for OSA is about 15% (N. C. Netzer et al., 1999; Reuveni et al., 2004; Skjodt, 2008). That means if the STOP-BANG is used only 15%, its sensitivity means about 13% of patients screened whereas the simple two or more high-risk diagnoses has the potential of identifying about 44% and obesity 69% of the patients in a PHC setting. When comparing specificities, the two or more high-risk diagnoses has a better performance than most of the screening tools with an 86% versus 56% of the STOP-BANG. Because of the high cost of

a polysomnogram, it is important to have a predictor with a high specificity, which means a high proportion of true negatives identified by the predictor. Therefore, by correctly identifying the true negatives, the costs of unnecessary polysomnograms are avoided.

Table 6: Sensitivity and Specificity Comparison for OSA Positive (AHI/RDI  $\geq$  5)

	<b>Sensitivity</b>	<b>Specificity</b>
Obesity	69%	68%
Two or more high-risk diagnoses	44%	86%
Epworth Sleepiness Scale	66%	48%
Berlin Questionnaire	54% to 86%	43% to 87%
STOP-BANG	84%	56%

Moreover, a cost analysis comparing the cost of false positives resulting in unnecessary polysomnograms against the cost of undiagnosed OSA can be used to justify the use of obesity or two or more high risk diagnoses as a means for screening to detect individuals who should be referred for a polysomnogram. There are significant direct health care costs associated with untreated OSA related to the aggravation of chronic diseases such as hypertension, diabetes mellitus type 2, and dyslipidemia (Calvin & Somers, 2009; Cuhadaroglu et al., 2009; Devulapally et al., 2009; Khayat et al., 2009). Also demonstrated in the literature is the cost of productivity loss due to sluggish thought process and neurocognitive impairment of untreated employees with OSA, which has been estimated to be about 37% (AlGhanim et al., 2008; Gurubhagavatula et al., 2008).

For the purpose of illustration, a cost analysis taking into consideration the cost of decreased work productivity can be used to illustrate that even when true cost of false negatives

are underestimated, the cost of false positives more than justify using obesity and two or more high-risk diagnoses to screen for OSA risk.

Suppose 100 patients are screened for OSA using obesity as a predictor, which has a false positive rate of 32%, and another 100 patients are screened using two or more high-risk diagnoses, which has a false positive rate of 14%. Estimating a yearly income of \$40,000, a decreased productivity of 37% is equivalent to a loss of \$14,800 for each patient. Considering that 70% of the 200 patients screened were positive for OSA, the annual productivity lost equals to \$2,072,000. The average polysomnogram costs about \$800 (Gurubhagavatula, 2008). Out of the 100 patients screened with obesity as a predictor, the cost of false positives would be \$25,600. For the other 100 patients screened with two or more high-risk diagnoses the false positive cost would be \$11,200. It is easy to visualize that the cost of false positive is insignificant before the potential of cost of not diagnosing the positive patients for OSA.

### **Recommendations**

The results of this study were significant to warrant further investigation to establish how well these findings replicate in other primary health care practice populations. Replication in other populations would support PCPs' wide use of these high-risk diagnoses and obesity to identify patients at risk for OSA. For instance, a prospective study for one year using samples from ten to twenty PHC practices in different states of the United States may be used to validate these findings. Future research should identify patients' race and ethnicity to support replication of findings in other populations. Additional analysis of these or future study data should be conducted to explore which combination of high-risk diagnoses would be more likely to predict a positive diagnosis of OSA. These results would provide a better understanding on how the use of

high-risk diagnoses and obesity would improve the screening of OSA in a PHC setting. Finally, research is needed regarding implementation of a screen based on obesity and/or two or more high risk diagnoses. Study sites for this research should include a mix of (a) electronic health records with a computerized alert triggered for the two or more high-risk diagnoses and for obesity, and (b) traditional paper charts where the identification of these risk factors would rely only on the healthcare provider's initiative.

There is a gap in the literature regarding high-risk diagnoses commonly seen in a PHC setting as predictors for OSA high-risk. Findings from the present study should be disseminated in several forms, such as professional publications, presentations at professional conventions and local seminars. The findings from this study should be communicated with the primary care practice community as well as the sleep medicine specialties.

### **Conclusion**

The need to find alternative ways for proper screening of OSA high-risk patients is evident from the continuous under-diagnosing of OSA. PCPs are positioned in a key place to improve the number of patients diagnosed and treated for OSA as they treat patients for common high-risk diagnoses (hypertension, diabetes mellitus type 2, dyslipidemia, arrhythmia, and coronary artery disease) on a daily basis. The use of high-risk diagnoses to identify the patients at risk for OSA in a PHC has the potential to improve OSA screening and diagnosis because it may be a simple and fast way for PCPs to identify these patients. In this study, the interaction term was not significant, indicating that the combination of obesity with two or more high-risk diagnoses does not improve prediction of patients with OSA. However, either obesity or two or more high-risk diagnoses were significant in the logistic regression analysis in predicting patients



at risk for OSA. The odds ratios without the interaction term in the analysis indicated over four-fold likelihood for OSA in patients with obesity or two or more high-risk diagnoses. There was no decrease in overall classification rate when the interaction term was dropped. The high predictive value found for two or more high-risk diagnoses (88%) in predicting OSA in this study, even considering some decrease due to lower incidence of OSA in a general adult population, may be important to encourage PCPs to order a polysomnogram for these patients. PCPs may have a reasonable degree of certainty when sending a patient for a polysomnogram knowing that the predictive value of using two or more high-risk diagnoses is significant for a positive OSA diagnoses. The ultimate goal of proper screening of high-risk patients leading to diagnosis and treatment of OSA is to improve patients' health conditions and their quality of life.

## APPENDIX A: EPWORTH SLEEPINESS SCALE

How likely are you to doze off or fall asleep in the situations described below, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:

0 = Would never doze

1 = Slight chance of dozing

2 = Moderate chance of dozing

3 = High chance of dozing

Situation Chance of dozing

1. Sitting and reading . . . . .
2. Watching TV . . . . .
3. Sitting, inactive in a public place (e.g. a theatre or a meeting) . . . . .
4. As a passenger in a car for an hour without a break . . . . .
5. Lying down to rest in the afternoon when circumstances permit . . . . .
6. Sitting and talking to someone . . . . .
7. Sitting quietly after a lunch without alcohol . . . . .
8. In a car, while stopped for a few minutes in the traffic . . . . .

Total . . . . .

A total score above 10 is abnormal, indicating high risk for OSA.

## APPENDIX B: BERLIN QUESTIONNAIRE

## Sleep Apnea

Height (m) \_\_\_\_\_ Weight (kg) \_\_\_\_\_ Age \_\_\_\_\_ Male / Female

Please choose the correct response to each question.

### Category 1

1. Do you snore?

- a. Yes
- b. No
- c. Don't know

*If you answered 'Yes':*

2. You snoring is:

- a. Slightly louder than breathing
- b. As loud as talking
- c. Louder than talking
- d. Very loud – can be heard in other rooms

3. How often do you snore?

- a. Almost every day
- b. 3-4 times per week
- c. 1-2 times per week
- d. 1-2 times per month
- e. Rarely or never

4. Has your snoring ever bothered other people?

- a. Yes
- b. No
- c. Don't know

5. Has anyone noticed that you stop breathing during your sleep?

- a. Almost every day
- b. 3-4 times per week
- c. 1-2 times per week
- d. 1-2 times per month
- e. Rarely or never

## Category 2

6. How often do you feel tired or fatigued after your sleep?

- a. Almost every day
- b. 3-4 times per week
- c. 1-2 times per week
- d. 1-2 times per month
- e. Rarely or never

7. During your waking time, do you feel tired, fatigued or not up to par?

- a. Almost every day
- b. 3-4 times per week
- c. 1-2 times per week
- d. 1-2 times per month
- e. Rarely or never

8. Have you ever nodded off or fallen asleep while driving a vehicle?

- a. Yes
- b. No

*If you answered 'Yes':*

9. How often does this occur?

- a. Almost every day
- b. 3-4 times per week
- c. 1-2 times per week
- d. 1-2 times per month
- e. Rarely or never

## Category 3

10. Do you have high blood pressure?

- Yes
- No
- Don't know

## APPENDIX C: SCORING BERLIN QUESTIONNAIRE

The questionnaire consists of 3 categories related to the risk of having sleep apnea. Patients can be classified into High Risk or Low Risk based on their responses to the individual items and their overall scores in the symptom categories.

### **Categories and Scoring:**

**Category 1:** items 1, 2, 3, 4, and 5;

Item 1: if 'Yes', assign **1 point**

Item 2: if 'c' or 'd' is the response, assign **1 point**

Item 3: if 'a' or 'b' is the response, assign **1 point**

Item 4: if 'a' is the response, assign **1 point**

Item 5: if 'a' or 'b' is the response, assign **2 points**

**Add points.** Category 1 is positive if the total score is 2 or more points.

**Category 2:** items 6, 7, 8 (item 9 should be noted separately).

Item 6: if 'a' or 'b' is the response, assign **1 point**

Item 7: if 'a' or 'b' is the response, assign **1 point**

Item 8: if 'a' is the response, assign **1 point**

**Add points.** Category 2 is positive if the total score is 2 or more points.

**Category 3** is positive if the answer to item 10 is 'Yes' or if the BMI of the patient is greater than 30kg/m<sup>2</sup>.

(BMI is defined as weight (kg) divided by height (m) squared, i.e., kg/m<sup>2</sup>).

**High Risk:** if there are 2 or more categories where the score is positive.



**Low Risk:** if there is only 1 or no categories where the score is positive.

**Additional Question:** item 9 should be noted separately.

## APPENDIX D: STOP-BANG SCORING QUESTIONNAIRE

1. Snoring: Do you snore loudly (louder than talking or loud enough to be heard through closed doors)? Yes / No
2. Tired: Do you often feel tired, fatigued, or sleepy during daytime? Yes / No
3. Observed: Has anyone observed you stop breathing during your sleep? Yes / No
4. Blood pressure: Do you have or are you being treated for high blood pressure? Yes / No
5. BMI: BMI more than 35? Yes / No
6. Age: Age over 50 yr old? Yes / No
7. Neck circumference: Neck circumference greater than 40 cm (16 inches)? Yes / No
8. Gender: Gender male? Yes / No

*High risk of OSA: Answering yes to three or more items*

*Low risk of OSA: Answering yes to less than three items*

## APPENDIX E: SPSS FILE FOR DATA COLLECTION



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