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This is to certify that the doctoral dissertation by

Mark Zellmer

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2010

ABSTRACT

Clinical Recognition of Obstructive Sleep Apnea in a Population-Based Sample

by

Mark R. Zellmer

M.A., College of St. Thomas, 1977
B.S., University of Iowa, 1983
B.A., Augsburg College, 1976

Dissertation Submitted in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Philosophy
Public Health

Walden University
November 2010

ABSTRACT

Obstructive sleep apnea (OSA), a disorder in which the airway intermittently collapses and obstructs during sleep, is associated with increased cardiovascular and cerebrovascular morbidity and mortality, increased risk of motor vehicle accidents, metabolic syndrome, hypertension, and depression. Treatment of OSA attenuates or reverses many of these associated risks. However, most cases of OSA are unrecognized and untreated. The two most recent studies using 1990s data found that only 6.5 – 15.4% of OSA cases, depending on severity, are clinically recognized in mixed gender populations. Based on a conceptual framework of improved physician awareness of OSA, and reduced diagnostic access bias with the increased availability of sleep laboratory services, increased OSA recognition since the 1990s was predicted. Study participants with clinically recognized OSA were identified using the resources of the Rochester Epidemiology Project, while the Berlin Questionnaire OSA high risk classification was used as a surrogate for prevalent OSA in this population. Analysis in a mixed gender population determined that OSA clinical recognition among those with prevalent OSA was 22.7 % (95% CI 19.6 – 25.8%) for mild or greater OSA severity leaving more than 75% of prevalent OSA clinically unrecognized and untreated in this population. Obesity and male gender were associated with increased likelihood of clinical recognition in bivariate and multivariate analyses, though even among obese men only 36.5% of OSA was clinically recognized. In order to support positive social change and address these inequities of OSA clinical recognition, strategies that enhance OSA recognition overall, and more specifically target recognition of OSA among women and the nonobese, should be developed and implemented. Further research regarding such strategies should consider whether they reduce OSA associated morbidity and mortality.

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DEDICATION

I would like to first dedicate this dissertation to my parents and grandparents. My grandparents had raised my parents on their farms where, in the 1940s encouraging them to go to high school, let alone college, was considered by some to be controversial when there was farm work to be done. Though neither of my parents lived to see me through my doctoral studies, the value they had placed on education over the years, and their encouragement to pursue ones dreams, provided an impetus for me to pursue doctoral education even as I was entering my 50s. Finally, I must dedicate this dissertation to my dear wife and our children who graciously allowed me the time and space to pursue, and now complete these studies and this dissertation.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1: INTRODUCTION TO THE STUDY

Background

Obstructive sleep apnea is a disorder in which the airway collapses causing an airway obstruction during sleep and recurrent arousals from sleep (Parish & Somers, 2004). The airway collapse and the resulting sleep interruptions produce the common symptoms of OSA that include excessive snoring, daytime sleepiness, and pauses in breathing reported by sleeping partners (Caples, Gami, & Somers, 2005; Parish & Somers, 2004).

Across the population, OSA of at least mild severity is not rare. In one early, classically cited, population-based epidemiologic study the prevalence of OSA with daytime symptoms was found to be 2% and 4% in women and men, respectively. However, the prevalence of at least mild OSA with or without symptoms was found to be 9% and 24% in women and men, respectively (Young et al., 1993). A later larger multicenter study demonstrated a similar prevalence with at least moderate OSA present in 11% and 25% of women and men, respectively (Young, Shahar et al., 2002). Overall those with sleep apnea are usually older, more obese, and more likely male with the prevalence higher among African-Americans and Asians (Young, Peppard, & Gottlieb, 2002).

OSA is associated with a variety of significant health problems including increased cardiovascular (Caples, Garcia-Touchard, & Somers, 2007) and cerebrovascular (Yaggi et al., 2005) morbidity and mortality, metabolic syndrome (Coughlin, Mawdsley, Mugarza, Calverley, & Wilding, 2004), hypertension (Duran,

Esnaola, Rubio, & Iztueta, 2001), and depression (Peppard, Szklo-Coxe, Hla, & Young, 2006). In addition, OSA is associated with increased risk of motor vehicle accidents (Young, Blustein, Finn, & Palta, 1997).

OSA Diagnosis and Treatment

The "gold standard" diagnostic technique for OSA is polysomnography (PSG) (Schlosshan & Elliott, 2004) which involves sleeping overnight in a laboratory with multichannel monitoring of brain, eye, and muscle activity, respiratory effort, heart rate, and blood oxygen saturation (Chesson et al., 1997). The diagnosis of OSA is then based on an evaluation of this array of physiologic parameters that determines the stage of sleep, number of apneas, hypopneas, and oxygen desaturations that occur and are then correlated with respiratory effort movements. The number of apneas plus the number of hypopneas occurring per hour of sleep represents the apnea-hypopnea index (AHI) which is a measure of OSA severity. OSA is generally considered present if the AHI is greater than five with daytime symptoms such as sleepiness, or greater than 15 with or without symptoms (Berry & Foster, 2005; Silber, Krahn, & Morgenthaler, 2004).

Continuous positive airway pressure (CPAP) is considered to be first-line therapy for those with moderate to severe OSA, especially those that have symptomatic daytime sleepiness (Giles et al., 2006; Kushida et al., 2006). CPAP devices use airflow generated by a fan and applied to the patient's airway by way of tubing and a nasal or oronasal mask to maintain the patency of the airway during sleep. Thus, CPAP functionally represents a pneumatic splint that prevents OSA-related airway obstruction (Hirshkowitz & Sharafkhaneh, 2005). A review of eight studies comparing OSA therapy with CPAP

against a placebo of sham CPAP therapy demonstrated effectiveness in reducing OSA severity (Gay, Weaver, Loube, & Iber, 2006).

There is evidence that the negative long-term effects of OSA are attenuated by treatment with CPAP. Several studies of cardiovascular morbidity and mortality have demonstrated reductions with CPAP therapy (Doherty, Kiely, Swan, & McNicholas, 2005; Milleron et al., 2004; Peker, Carlson, & Hedner, 2006). Unfortunately the ability to adhere to CPAP therapy among those for whom it has been prescribed has been limited and variable. A classic study (Kribbs et al., 1993) demonstrated that only 46% were able maintain use of CPAP at four or more hours per night. More recent studies have shown similar adherence rates ranging from 31% (Richards, Bartlett, Wong, Malouff, & Grunstein, 2007) to about 48% (Joo & Herdegen, 2007) with a usual pattern of care.

Historic Clinical Under Recognition of OSA

There is evidence that a significant portion of those with OSA historically have been clinically undiagnosed. However, the extent of this under diagnosis has not been assessed since the 1990s. In the 1980s it was thought that less than 1% of prevalent OSA had been diagnosed clinically (Dement, 1993; Strohl & Redline, 1996). There are only two population-based studies that evaluated the portion of prevalent OSA that was clinically diagnosed, both based on data collected in the 1990s (Kapur et al., 2002; Young, Evans, Finn, & Palta, 1997). These studies demonstrated that 2 – 18% of OSA had been clinically diagnosed varying based on gender and OSA severity. Thus, from the 1980s to the 1990s there had been some increase in the proportion prevalent OSA that

was clinically diagnosed. However, most OSA, 82 – 98%, remained undiagnosed in the 1990s.

The under recognition of clinical OSA has been identified by the Institute of Medicine as an unmet public health problem (Colten & Altevogt, 2006). Among the potential explanations for limited clinical OSA recognition are the following: (a) limited OSA awareness by physicians (Papp, Penrod, & Strohl, 2002; Reuveni et al., 2004; R. Rosen & Zozula, 2000), (b) limited access to sleep laboratories and specialists (Flemons, Douglas, Kuna, Rodenstein, & Wheatley, 2004; Morgenthaler et al., 2006), and (c) the expensive and intrusive nature of laboratory-based PSG (Colten & Altevogt, 2006; van de Mortel, Laird, & Jarrett, 2000).

Changes in health professional education, access to PSG, and the development of new OSA diagnostic techniques not requiring PSG are described in chapter 2. These changes could all provide a basis for an increase in OSA clinical recognition in the past decade. However, there has been no research measuring the rate of OSA clinical recognition subsequent to the 1990s.

In the first of the two studies evaluating clinical diagnosis of OSA, the following characteristics were associated in bivariate analysis with a greater likelihood having been diagnosed: male gender, previous cardiovascular disease, age, Caucasian race, and higher socioeconomic status based on income and education (Young, Evans et al., 1997). In the second of these studies (Kapur et al., 2002) bivariate analysis identified male gender, history of hypertension, higher body mass index (BMI), college graduation, and a lower high density lipoprotein (HDL) cholesterol levels as more common among those

diagnosed. However, in multivariate regression analyses, only gender and BMI remained predictive of a clinical diagnosis in this study.

Problem Statement

OSA is associated with increased cardiovascular and cerebrovascular morbidity and mortality (Caples et al., 2007; Yaggi et al., 2005). The diagnosis and subsequent treatment of OSA attenuates this long-term morbidity and mortality (Doherty et al., 2005; Milleron et al., 2004; Peker et al., 2006). However, most OSA is clinically unrecognized and untreated (Dement, 1993; Kapur et al., 2002; Strohl & Redline, 1996; Young, Evans et al., 1997). There is some evidence that clinical OSA recognition in the 1990s had improved from the 1980s, but still only 2 – 18% of OSA was diagnosed (Kapur et al., 2002; Young, Evans et al., 1997). Since the 1990s there have been improvements in several of the factors associated with under diagnosis (Marshall et al., 2007; Namen et al., 2002; Zozula, Rosen, Jahn, & Engel, 2005). The proportion of prevalent OSA that has been clinically diagnosed has not been assessed since a previous analysis of data obtained in 1995 – 1998 (Kapur et al., 2002). With this most recent analysis of the clinical recognition of OSA having been done more than ten years ago, factors predictive of clinical recognition have not been evaluated following the changes of the past decade.

Nature of the Study

An expansion of an existing population-based study was used to determine the proportion of prevalent OSA that had been diagnosed clinically, and identify predictors of clinical diagnosis. The longitudinal Prevalence of Asymptomatic Ventricular Dysfunction Study (PAVD Study) (Redfield et al., 2003) was initiated in 1997. This

study identified a population-based sample randomly selected from the residents of Olmstead County, Minnesota who were at least 45 years old on January 1, 1997. In the PAVD study OSA risk was characterized using a modified Berlin Questionnaire (Netzer, Stoohs, Netzer, Clark, & Strohl, 1999). Data collection that would allow the OSA risk characterization, either high or low, for all PAVD round two participants, was completed in 2004 as part of the ongoing study.

This study used the resources of the Rochester Epidemiology Project (Melton, 1996) to link PAVD participants and their OSA risk with their clinical records. This matching allowed the determination of (a) the frequency of clinical evaluation for OSA, (b) the prevalence of a clinical diagnosis of OSA among those at high risk for OSA, and (c) the differential characterization of those diagnosed and undiagnosed with OSA among those at high risk for the disorder.

Thus, the research questions addressed by this study are as follows:

1. What proportion of those at high risk for OSA based on the Berlin Questionnaire have been clinically evaluated for OSA?
2. What is the prevalence of clinically diagnosed OSA among those at high risk for OSA based on responses to the Berlin Questionnaire?
3. Has the prevalence of clinically diagnosed OSA increased in the past decade?
4. What factors were predictive of the clinical diagnosis of OSA among those at high risk of OSA?

The hypotheses (H_A) which were evaluated by this study include the following:

1. There is a portion of those at high risk for OSA that has not been clinically evaluated.
2. There is a portion of those at high risk for OSA that has not been clinically diagnosed.
3. There has been an increase in the proportion of prevalent OSA that is diagnosed clinically compared to the mid-1990s.
4. Among those at high risk for OSA the following characteristics will be more common among those with a clinical diagnosis of OSA than among those undiagnosed: age, male gender, higher BMI and higher socioeconomic status.

Thus the null hypotheses (H_0) for this study were the following:

1. There is no difference between the population at high risk for OSA and those that have been clinically evaluated.
2. There is no difference between the population at high risk for OSA and those that have been clinically diagnosed.
3. There has been no change in the proportion of prevalent OSA that is diagnosed clinically compared to the mid-1990s.
4. Among those at high risk for OSA there is no difference regarding the following characteristics among those with a clinical diagnosis of OSA than among those undiagnosed: age, gender, BMI, and socioeconomic status.

Purpose of the Study

The purpose of this study was to determine if the proportion of OSA that is clinically recognized had changed since the mid-1990s. Those who are at high risk for

OSA based on the modified Berlin Questionnaire (Netzer et al., 1999) were identified by the use of the instrument in the PAVD study (Redfield et al., 2003). Through matching of this sample with clinical records those with clinically diagnosed OSA will be identified. Factors predictive of clinical diagnosis were identified.

In this study the independent variables include OSA risk based on the modified Berlin Questionnaire and demographic variables including age, gender, BMI, socioeconomic status, and other clinical parameters assessed in the PAVD study. The dependent variable was the clinical diagnosis of OSA based on a review of clinical records.

Theoretical Basis

The under recognition of OSA has been partly attributed to limited physician awareness of the disorder. The clinical diagnostic process has been studied for many years and has been described as an iterative process of hypothesis generation followed by deductive hypothesis testing. Together, these processes are referred to as the hypothetico-deductive strategy (Round, 2001). Theory of hypothesis generation requires that the diagnostician have some prior knowledge of a disorder in order for that disorder to be among the diagnostic hypotheses generated (Bockenholt & Weber, 1993; Round, 2001). Simply put, clinicians are unable to diagnose disorders about which they have no awareness. Thus, if there is increased awareness of OSA among physicians, one would predict an increased prevalence of clinical recognition.

The theory of diagnostic access bias has been defined as the nonidentification of patients "because they have no access to diagnostic process" (Choi & Pak, 2000, p. 76).

In applying this theory to the clinical recognition of OSA, the lack of access to PSG (which is the primary clinical diagnostic technology for OSA) would be expected to limit OSA clinical recognition. Therefore the clinical recognition of OSA would be expected to increase as access to PSG technology increases.

One qualitative study of patients undergoing PSG (van de Mortel, Laird, & Jarrett, 2000) generated a satisfaction-compliance theory which states "The degree of satisfaction with the sleep studies experience is to some degree a predictor of compliance" (p. 167). If sleep centers have been at all successful in pursuing improved patient satisfaction with PSG since the completion of the original OSA clinical recognition studies (Kapur et al., 2002; Young, Evans et al., 1997), this theory would predict increased compliance with completing PSG, and thus a higher prevalence of clinically recognized PSG.

In summary, a theoretical basis exists relative to (a) physician OSA awareness, (b) PSG diagnostic access, and (c) satisfaction-compliance theory for increased prevalence of OSA clinical recognition since its previous assessments based on data collected about 10 years ago.

Operational Definitions

For the purposes of this study operational definitions and acronyms as described below are used.

Apnea: the termination of airflow at the mouth or nose for 10 seconds or more (Berry & Foster, 2005).

AHI: Apnea-hypopnea Index, the total number of apneas and hypopneas occurring per hour of sleep as quantified by polysomnography (Berry & Foster, 2005).

BMI: Body mass index, an index of obesity calculated as the weight in kilograms divided by the height in meters squared (Thomas, 1997)

Clinically diagnosed obstructive sleep apnea: a patient whose clinical records indicate that their healthcare provider had made the diagnosis of sleep apnea typically based on polysomnography.

Hypopnea: a reduction in thorocoabdominal abdominal respiratory movement or airflow that is 30% or more less than baseline associated with an oxygen desaturation that is four per cent or more less than baseline during polysomnography (Meoli et al., 2001)

CPAP: Continuous Positive Airway Pressure, a breathing support device used primarily at night involving transmission of air pressure produced by a fan through tubing and a nasal or oro-nasal mask producing a pneumatic airway splint designed to prevent airway obstruction (Hirshkowitz & Sharafkhaneh, 2005).

OSA: Obstructive Sleep Apnea, a sleep-related breathing disorder in which the upper airway collapses during sleep producing an obstructed airway. Respiratory efforts continue despite the obstruction often leading to arousal due to falling oxygen saturation levels (Berry & Foster, 2005).

OSA Risk: Obstructive Sleep Apnea Risk, in the context of this study OSA risk is determined based on the Berlin Questionnaire, a previously validated instrument that classifies respondents in a binary manner as “high” or “low” risk (Netzer et al., 1999).

PAVD Study: Prevalence of Asymptomatic Ventricular Dysfunction Study, a longitudinal population-based study in Olmstead County, Minnesota primarily to assess the cardiac dysfunction over time that now also includes an assessment of obstructive sleep apnea risk (Redfield et al., 2003).

PSG: Polysomnography, sleeping overnight in an observational clinical laboratory with a multichannel monitoring system for brain, eye, and muscle activity, respiratory efforts, heart rate, and blood oxygen saturation (Chesson et al., 1997).

RDI: Respiratory Disturbance Index, generally equivalent to the AHI, though some centers use a respiratory effort-related arousal rather than hypopneas to calculate this index (Berry & Foster, 2005).

Assumptions and Limitations

Several assumptions are inherent in the design of this study. This study used a modified Berlin Questionnaire (BQ) as the method of identifying those with OSA. High risk for OSA was used as a proxy for prevalent OSA making the assumption that all of those identified as at high risk for OSA actually have the disease. The basis for this assumption is the high positive and negative predictive values for the BQ from the originally published validation study (Netzer et al., 1999). Further analysis of the BQ, along with its modification and diagnostic performance in multiple subsequent studies is provided in the literature review. Thus, it is important to recognize the weakness of this assumption, namely, that those classified as high risk by the BQ represent all of those with prevalent OSA. Though the definitive measure of prevalence would be performance of PSG on the entire sample, such an evaluation with a sample size of over 1400 patients

would be cost prohibitive. There will be opportunity to assess the diagnostic performance of the BQ in this sample based on the results of the polysomnography studies done clinically; however diagnostic performance based on these results will itself be subject to test verification bias (Roger et al., 1997).

The random selection and longitudinal nature of the PAVD study (Redfield et al., 2003) that provided the population-based sample for this study requires consideration of assumptions regarding participation bias and attrition. Participation bias in the original sample in round one was considered previously with little evidence of impact on overall results (Jacobsen et al., 2004). A further analysis of round two participation bias is presented in chapter 4.

The outcome measure for this study was the clinical diagnosis of OSA and thus will assume consistency of diagnostic criteria and methodology in making that diagnosis. However, in making the diagnosis of OSA it has been recognized that there is variability in the gold standard PSG sensors (Redline & Sanders, 1999), the definition of hypopnea (Tsai, Flemons, Whitelaw, & Remmers, 1999), patient night-to-night variability (Bittencourt et al., 2001), and inter-rater variation (Loredo, Clausen, Ancoli-Israel, & Dimsdale, 1999). Some of this variation has been addressed by recently published PSG scoring criteria (Redline et al., 2007). With the clinical diagnoses for the study coming from primarily two sleep laboratories involving multiple clinicians over a period of years there will be variation in the basis for the diagnoses. Chapter 4 presents an analysis of the clinical diagnosis in relationship to a PSG diagnosis based on AHI alone. Since this

outcome measure is by its definition a measure of the clinical process of care over time, this variation is expected and acceptable.

This population-based sample was drawn from the Olmstead County, Minnesota population in 1997. Olmsted County had been 95.6% Caucasian in 1990, 90.3% in 2000, and more recently, 88.9% in 2006. In 2000 the Olmsted County adult population (age 18 and over) was 99.1% Caucasian (US Census Bureau, 2007). The sample for this study having been drawn from those ages 45 and older in 1997 was by self-report 97.9% Caucasian. This appears representative of the county at the time of sampling. However, because less than 3% of the sample was non-Caucasian, the results of the study are interpreted in light of this limited racial diversity.

Significance of the Study

In a recent monograph (Colten & Altevogt, 2006) OSA was identified as a public health problem by the Institute of Medicine which recommended that there be support for "additional surveillance and monitoring of sleep patterns and sleep disorders." (p. 11). This study measured changes in the clinical recognition of OSA in the past decade during which time enhanced physician awareness of OSA and improved access to PSG may have increased the likelihood of clinical recognition. This information is of value to public health officials and the health care system for allocation and organization of the systems that evaluate and treat OSA in order to improve health outcomes.

The Pickwickian syndrome, an early term for what is now recognized as OSA, was epitomized by Fat Joe from Charles Dickens and represents the classic description characteristics associated with sleep apnea (Conti, Conti, & Gensini, 2006). Indeed

snoring, obesity, male gender, and age are all considered to be among the risk factors for the disorder (Young, Peppard et al., 2002). Previous studies evaluating the clinical recognition of OSA (Kapur et al., 2002; Young, Shahar et al., 2002) have suggested that these factors, along with socioeconomic status as measured by income and education, increase the likelihood of clinical recognition. Because this study identified the characteristics of those both likely to and unlikely to be clinically diagnosed with OSA, those factors are useful in guiding future strategies for clinical recognition. This study represents a timely assessment of progress related to OSA clinical diagnosis in the past decade and provides information useful in (a) guiding future diagnostic strategies, particularly for those more likely to be previously undiagnosed; and (b) resource allocation to address OSA as public health problem.

Summary

OSA is a sleep-related breathing disorder that is associated with significant cardiovascular and cerebral vascular morbidity and mortality. Treatment with CPAP does attenuate this increased morbidity and mortality, but adherence to CPAP is challenging and limited. More importantly, most OSA is undiagnosed. Previous research has shown that no more than 18% of prevalent OSA was clinically diagnosed in the 1990s. OSA along with other sleep-related problems has been identified as public health problem by the Institute of Medicine.

In the past decade there have been efforts to increase health professional awareness and PSG diagnostic capacity for OSA. Thus, this study represents a timely evaluation of the impact of these efforts on OSA clinical diagnosis. In addition, the study

differentially identifies characteristics of those likely and unlikely to be among those with clinically diagnosed OSA.

The study identified those at high risk for OSA using the previously validated BQ in a population based sample from Olmsted County, Minnesota. The sample was matched with clinical records including PSG to determine the clinical diagnostic rate and factors that predict having clinically diagnosed OSA.

In chapter 2 a literature review is presented which addresses in greater detail OSA risk factors, diagnostic considerations, and treatment characteristics. The literature regarding validation, modification, and performance of the BQ as a screening instrument for OSA is also be reviewed. Previous research estimating OSA clinical recognition is evaluated along with factors thought to contribute to under recognition.

The methods used in this study are described in chapter 3. This includes the population sampling and OSA screening methods used as part of the ongoing PAVD research. The method of identifying those with clinical PSGs and OSA using the resources of the Rochester Epidemiology Project (REP) (Melton, 1996) are also described.

Analyses of the study's data related to participation bias, validation of the REP methods for identifying those participants that had undergone PSG and were clinically recognized with OSA, and analysis of the application of the BQ are presented in chapter 4. The results addressing the four research questions are also presented.

Finally in chapter 5 these results are interpreted along in light of the study's strengths and weaknesses. Based on these results recommendation for action and further research regarding OSA clinical recognition are made.

CHAPTER 2: LITERATURE REVIEW

Introduction

A review of the literature related to the epidemiology, diagnosis, and treatment of obstructive sleep apnea (OSA), previous assessments of the prevalence of the clinical diagnosis OSA, the use of the BQ for assessing OSA risk, and the use of patient clinical records for epidemiologic research is provided in this chapter.

Organization of the Literature Review

This chapter is organized in a series of five sections designed to systematically provide readers background necessary for the study's context, a review of previous studies of the under diagnosis of OSA, and the nature of the study's instrument and methods. A background review of the epidemiology, diagnosis, and treatment of OSA is provided in the first section of this chapter and is the scientific context for this study's analysis of OSA clinical recognition. A critical review of the previous assessments of the OSA under diagnosis, a description of factors potentially explaining that under diagnosis, and the changes that have occurred regarding these factors are presented in the second section. A review of the development, use, and performance characteristics of the BQ as a tool for identifying those at high risk for OSA is presented in the third section. The a review of the use of patient clinical records for epidemiologic research, in particular the structure and resources of the Rochester Epidemiology Project is presented in section four. Finally a review of the Prevalence of Asymptomatic Ventricular Dysfunction study (Redfield et al., 2003) which had created the population-based sample in which the prevalence of clinically recognized OSA was evaluated is presented in the fifth section.

Literature Search Strategies

The identification of publications for this review has been carried out through multiple iterative searches using primarily the MEDLINE database of the National Library of Medicine (NLM) searched with the proprietary search interface known as the Ovid Web Gateway™ (Ovid Technologies, Inc., Norwood, MA). In addition, the EMBASE, CINAHL, and PsycINFO databases were also used for some selected topics. Most literature regarding OSA was identified from among over 5600 publications indexed under the NLM's medical subject heading (MeSH) "Sleep Apnea, Obstructive" although some searches were expanded to include citations indexed under the MeSH terms "Sleep Apnea Syndromes" which together include nearly 17,000 citations. Additional searches using the terms "Continuous Positive Airway Pressure" with over 2200 citations, or "Polysomnography" also with over 10,000 citations were carried out. In addition, the reference lists from retrieved papers, review articles, and relevant texts were searched to identify citations not otherwise identified. Papers identified were most commonly retrieved through the digital resources of the Mayo Clinic Libraries ("Mayo Clinic Libraries," 2007) including interlibrary loan, with supplementation from the Walden University Library, and personal subscriptions providing access to the journal *Sleep*, and the *Journal of Clinical Sleep Medicine*. Generally only English language papers were reviewed, although for selected topics uniquely addressed by German or Italian papers these were also reviewed. Except for topics related to the historical development of OSA science, review was largely limited to papers published since 1990.

Epidemiology, Diagnosis, and Treatment of OSA

Prevalence of Obstructive Sleep Apnea

In the past 27 years there have been at least 27 papers (see Table 1) that have estimated the prevalence of obstructive sleep apnea in various populations. These studies have been done in several countries including Italy, Spain, Sweden, Hong Kong, Korea, India, the United Kingdom, Australia, New Zealand, and Brazil in addition to the United States. In comparing the reported prevalence from these studies there is substantial variability with a range from less than 1% (Lavie, 1983) to over 50% in adult, nonelderly, male populations (Redline, Schluchter, Larkin, & Tishler, 2003). Previous commentators have suggested that this variability could be attributed to variation in the definition used for the disorder, study design, sample selection, physiologic parameter measurement methods, and the day-to-day variability of these sleep parameters (Lindberg & Gislason, 2000; Young, Peppard et al., 2002).

OSA is a chronic condition along a continuum of severity in the symptoms and physiologic measures used to define the disorder including snoring, hypersomnolence, sleep fragmentation, apneas, hypopneas, blood oxygen saturation, and sleep arousal. There are several syndromes described along this continuum including sleep apnea (SA), obstructive sleep apnea syndrome (OSAS), sleep apnea hypopnea syndrome (SAHS), and upper airway resistance syndrome (UARS), all of which can be considered to be part of the global continuum of sleep-related breathing disorders (SBD). For any one of these syndromes there is considerable variation in the study definition used leading to divergent reports of prevalence (Lindberg & Gislason, 2000; Young, Peppard et al., 2002).

Table 1

Studies Reporting Population Prevalence of Obstructive Sleep Apnea in Chronological Order

First Author	Year Published	Location	Gender	Age	Study Design	Sleep Monitor	OSA Criteria	OSA Prevalence (%)		
								All	♂	♀
Lavie	1983	Israel	Men	≥18	NP 2-stage	L-PSG	AI≥10		0.9[b]	
Berry	1986	Florida	Men	>30	NP 1-stage	L-PSG	AHI≥5		13	
Gislason	1988	Sweden	Men	30-70	PB 2-stage	L-PSG	RD>30		1.3[b]	
Cirignotta	1989	Italy	Men	30-70	PB 2-stage	L-PSG	AHI≥5 AHI≥10		4.0[b] 2.7[b]	
Ancoli-Israel	1991	San Diego	Both	≥65	PB 1-stage	H-PSG	AI≥5 RDI≥10	24 62	28 70	20 56
Stradling	1991	United Kingdom	Men	35-65	NP 2-stage	L-PSG	ODI>5 sev. OSA	5 0.3[b]		
Young	1993	Wisconsin	Both	30-60	PB 2-stage	L-PSG	AHI≥5 AHI≥5[a]		24 4	9 2
Redline	1994	Cleveland	Both	≥16	NP	H-PSG	RDI≥15		26	13
Olson	1995	Australia	Both	35-70	PB 1-stage	PulOx+	RDI≥15	3.6[b]	25.9	7.7
Kripke	1997	San Diego	Both	40-65	PB 1-stage	PulOx	ODI≥20		9.3	5.2
Ohayon	1997	United Kingdom	Both	≥15	PB 1-stage	Qust-SE	ICSD	1.9	3.5	1.5
Bixler	1998	Pennsylvania	Men	≥20	PB 2-stage	L-PSG	AHI≥10 AHI≥10[a]		10.5 3.3	
Netzer	1999	Cleveland	Both	≥15	NP 2-stage	H-PSG	RDI≥5 RDI≥15	66 38		
Bixler	2001	Pennsylvania	Both	≥20	PB 2-stage	L-PSG	AHI≥15 AHI≥10[a]		7.2 3.9	2.2 1.2
Duran	2001	Spain	Both	30-70	PB 2-stage	L-PSG	AHI≥5 AHI≥10 AHI≥10[a]		26.2 19.0 3.4	28.0 14.9 3.0
Young	2002	Multicenter USA	Both	39-99	PB 2-stage	H-PSG	AHI≥15		25	11

Netzer	2003	Cleveland	Both	≥15	NP	Qust-B	HR	32.3	37.9	27.8

(table continues)

First Author	Year Published	Location	Gender	Age	Study Design	Sleep Monitor	OSA Criteria	OSA Prevalence (%)		
								All	♂	♀
Kim	2004	Korea	Both	40-70	PB 2-stage	H-PSG	AHI≥5		27.1	16.8
							AHI≥5 [a]		4.5	3.2
							AHI≥10		18.9	6.7
Udwadlia	2004	India	Men	35-65	PB 2-stage	H-PSG	AHI>5		19.5	
							AHI>5 [a]		7.5	
Roehrs	2006	Detroit	Both	31-40	NP 1-stage	L-PSG	RDI≥5		12.5	0.5
							RDI≥10		5.2	0
Sharma	2006	India	Both	30-60	PB 2-stage	L-PSG	AHI>5	13.7	19.7	7.4
							AHI>5 [a]	3.6	4.9	2.1
Hiestand	2006	continental USA	Both	≥18	PB 1-stage	Qust-B	HR	26	31	21
Reddy	2009	Delhi, India	Both	30-65	PB 2-stage	L-PSG	AHI≥5	9.3	13.5	5.5
Mihaere	2009	New Zealand	Both	30-59	PB 1-stage	H-PSG	RDI≥5		12.5	3.4
Tufik	2010	Sao Paulo, Brazil	Both	20-80	PB 3-stage	L-PSG	AHI≥5 [a]	32.9	40.6	26.1

(table continues)

Notes.

AHI: Apnea Hypopnea Index calculated as the number of apneas plus the number of hypopneas divided by the number of hours of sleep; AI: Apnea Index calculated as the number of apneas divided by the number of hours of sleep; H-PSG: Home polysomnography, a portable device recording system that measures a subset of the typical laboratory polysomnography parameters in the participant's home without an attendant present with later data scoring; HR: High risk: defined by the BQ (Netzer et al., 1999); ICSD: International Classification of Sleep Disorders as defined by symptoms in groups A, B, and C (Thorpy, 1990), p. 57); L-PSG: Laboratory polysomnography, an in laboratory monitoring of a complete montage of sleep and breathing parameters carried out with an attendant and both real-time and post data collection analysis and scoring; NP: nonpopulation-based sampling design; ODI: oxygen desaturation index, calculated as the number of oxygen desaturations greater than 4% below baseline divided by the number of hours of sleep; OSA: Obstructive Sleep Apnea; PB: population based sampling design; PulOx: pulse oximetry monitoring including recording continuous oxygen saturation and audio recording of breathing sounds; PulOx+: pulse oximetry monitoring recording including continuous oxygen saturation, and audio recording of breath sounds with the addition of chest and abdominal movement sensor recordings Qust-B: questionnaire evaluation using the BQ (Netzer et al., 1999; "Reprinting of the Berlin Questionnaire," 2000); Qust-SE: questionnaire evaluation using the computerized Sleep-Eval knowledge based system (Ohayon, Guilleminault, Priest, & Caulet, 1997); RD: the number respiratory disturbances per night without regard to the number of hours of sleep; RDI: Respiratory Disturbance Index calculated as the number of respiratory disturbances divided by the number of hours of sleep; sev. OSA: severe OSA as defined by long-term symptoms, and AHI≥20;

[a] these criteria require a constellation of daytime symptoms in addition to the minimum required AHI;

[b] considered the lower limit of prevalence with the assumption that all OSA in the population was identified in the studied sample.

As examples of this variability, Lavie's (1983) early report of the prevalence of sleep apnea uses the apnea index (AI) which was defined by apneas alone with a criterion of at least 10 per hour of sleep. In contrast, a later paper by Redline and colleagues (2003) which reports the highest prevalence, used the respiratory disturbance index (RDI) which included both apneas and hypopneas with the later defined as a "discrete reductions in airflow or chest impedance, lasting at least 10 seconds and associated with at least a 2.5% fall in oxygen saturation" (p. 704). Here the criterion for OSA was at least five apneas and hypopneas per estimated hour of sleep with no requirement for daytime symptoms. Thus, the particular syndrome evaluated and the specific criterion used to define that syndrome impact the reported prevalence of the disorder.

A variety of methods for sample selection and identification of OSA have been used, often including a two-stage design in which a questionnaire or interview screening process was used to identify a segment of the population with a high likelihood of sleep disordered breathing. Then participants in this high risk group are selected (or in some studies, over-sampled for study along with a sample from the remaining lower risk portion of the population) to undergo a more definitive evaluation for the actual presence of a SBD syndrome based on the definition used in the study. Some papers using a multi-stage method have reported a population prevalence based on a weighting of the prevalence obtained from high and low risk groups (E.O. Bixler et al., 2001; E.O. Bixler, Vgontzas, Ten, Tyson, & Kales, 1998; Tufik, Santos-Silva, Taddei, & Bittencourt, 2010). By contrast, other papers have made the assumption that all those with SBD in the population are detected by the screening questionnaire and did not definitively study any participants in the low risk population segment. In recognition that the questionnaires

used are neither 100% sensitive nor 100% specific, several of these papers have reported the resulting prevalence as the lower limit of the population prevalence (Duran et al., 2001; Gislason, Almqvist, Eriksson, Taube, & Boman, 1988; Lavie, 1983; Olson, King, Hensley, & Saunders, 1995; Stradling & Crosby, 1991).

Though many of these papers have used a population based sampling method with either a single or two-stage case detection method, other papers have not used population-based sampling. For example, Redline and colleagues (1994) used a population consisting of relatives and neighbors of participants with known sleep apnea. Two other studies (Netzer et al., 2003; Netzer et al., 1999) used a convenience sample of patients presenting to selected primary care physicians offices. Though the samples resulting from these methods may have a resemblance to the general population in the areas from which they are drawn, that resemblance might be considered accidental rather than by design.

Studies have used a variety of testing methods to identify OSA in their sampled populations. As described in the "Sleep Monitor" column of Table 1, about half of the studies reviewed here used the clinical gold-standard of polysomnography conducted in the sleep laboratory monitored by a trained sleep laboratory technician (L-PSG: laboratory PSG). About one-third of the studies used a type of the less expensive portable polysomnography carried out in the participants' homes without the benefit of an attending sleep laboratory technician (H-PSG: Home PSG). A few studies have also used detection methods based primarily on oxygen saturation monitoring (Kripke et al., 1997; Olson et al., 1995) or a purely questionnaire based detection method (Hiestand, Britz, Goldman, & Phillips, 2006; Netzer et al., 2003; Ohayon et al., 1997). Thus, these varying

techniques may generally detect those with a syndrome along the SDB continuum, the exact syndrome, and associated severity reported is variable for these methods.

A number of these studies (E.O. Bixler et al., 2001; Ip et al., 2001; Kim et al., 2004; Sharma, Kumpawat, Banga, & Goel, 2006; Udwadia, Doshi, Lonkar, & Singh, 2004; Young et al., 1993) have reported population prevalence using a particular AHI or RDI criterion both with and without regard to daytime symptoms for the particular AHI criterion. In all of these studies the symptomatic prevalence is much lower, ranging from about one sixth to one half of the prevalence when daytime symptoms are not included in the criteria.

The inclusion of a daytime symptom requirement in the research diagnostic criteria for OSA by the American Academy of Sleep Medicine Task Force (Flemons et al., 1999) was suggested as an "operational definition" (p. 670) but it was recognized that there were no studies validating this criterion. There is evidence that adverse long-term outcomes result from SDB regardless of the presence of daytime symptoms. The two largest OSA prevalence cohorts (Young et al., 1993; Young, Shahar et al., 2002) have demonstrated increased risk of hypertension for those with mild OSA without regard to daytime symptoms (Nieto et al., 2000; Young, Peppard et al., 1997). Another large study (E. O. Bixler et al., 2000) demonstrated associations of SDB with hypertension even for those with AHI<5, again without regard for daytime symptoms. There is also evidence that those with mild SDB and no pathologic sleepiness demonstrate reduced AHI (a measure of OSA severity) and improved mood, functional status, general health, and energy with standard CPAP treatment for OSA (Redline et al., 1998).

Daytime sleepiness is associated with increased OSA severity as demonstrated in the large Sleep Heart Health Study where the Epworth Sleepiness Scale (ESS) showed a statistically significant correlation with RDI severity (Gottlieb et al., 1999). In addition, sleepiness has been found to be predictive of diminished cardiac output even when OSA severity, as measured by RDI, was held constant (J. B. Choi et al., 2006). Thus, daytime sleepiness appears to be a marker of OSA disease severity, though as a binary marker, sleepiness seems to be a poor criterion for the presence or absence of OSA.

Analysis of the varying prevalence demonstrated in Table 1 shows that if one considers studies with population based samples that used an AHI or RDI criterion of greater than or equal to five without a daytime sleepiness requirement eight of the ten such studies (Ancoli-Israel et al., 1991; Cirignotta et al., 1989; Duran et al., 2001; Ip et al., 2001; Kim et al., 2004; Mihaere et al., 2009; Reddy et al., 2009; Sharma, Kumpawat et al., 2006; Udwadia et al., 2004; Young et al., 1993) report a rather consistent male OSA prevalence of 12.5% – 28%. The two papers among these eight that substantially deviate from this population prevalence include one which selected for PSG study only 40 every-night snorers with the assumption that all those with OSA snore (Cirignotta et al., 1989). The remaining study (Ip et al., 2001) made a similar conservative assumption that there was no OSA among those who did not undergo PSG. Thus, these two studies (Cirignotta et al., 1989; Ip et al., 2001) used analytic methods that would under-report OSA.

The six other population based studies in Table 1 include those that used criteria involving either AHI cut-off values of 10 or more (E.O. Bixler et al., 2001; E.O. Bixler et al., 1998; Young, Shahar et al., 2002), or were based other indexes including oxygen

desaturation index (ODI) (Kripke et al., 1997) and total respiratory disturbances during the night (RD) (Gislason et al., 1988). Thus, these studies might be expected to under-represent the OSA prevalence that would be expected based on an AHI cut-off of 5. Despite these differences one of these studies reports a male OSA prevalence of 25.9% (Olson et al., 1995), similar to the range noted previously. Thus, it seems that a population prevalence estimate of 19 – 25% for OSA in males using an AHI greater than or equal to 5 without a daytime sleepiness requirement represents a rather consistent estimate across these studies.

Reviews of the gender prevalence of OSA and SDB have suggested that the male to female ratio is in the range of 1.5 – 3:1 (Jordan & McEvoy, 2003; Kapsimalis & Kryger, 2002). Similar to the male analysis described above, there are six population based studies that report a female prevalence using an AHI or RDI greater than or equal to five without a daytime sleepiness requirement (Ancoli-Israel et al., 1991; Duran et al., 2001; Kim et al., 2004; Sharma, Kumpawat et al., 2006; Young et al., 1993; Young, Shahar et al., 2002). These studies show male to female ratios that range from 0.9 – 2.7:1 with the one study showing a greater prevalence for females compared to males having been conducted in Spain (Duran et al., 2001). For the other population based studies that report prevalence for both genders using other OSA criteria, the male to female ratios range from 1.8 – 3.4:1 (E.O. Bixler et al., 2001; Kripke et al., 1997; Olson et al., 1995). Though the origins of these differences are not well established, there is the suggestion that women may less commonly present with classical symptoms leading to relatively greater under-recognition (Jordan & McEvoy, 2003; Kapsimalis & Kryger, 2002; Young, Hutton, Finn, Badr, & Palta, 1996).

OSA Symptoms and Risk Factors

The most common symptom associated with OSA is snoring which has been found in as many as 97% of those with OSA (Whyte, Allen, Jeffrey, Gould, & Douglas, 1989). Among men with OSA about 85% report habitual snoring defined as snoring at least three nights per week (Flemons, Whitelaw, Brant, & Remmers, 1994; Rowley, Aboussouan, & Badr, 2000), and about 90% of those with OSA having at least some snoring regardless of gender (Rowley et al., 2000). However, some reports acknowledge that snoring is not present in significant portions of some populations with OSA such as a Danish study which found that 48% women and 19% of men with OSA did not report snoring (Jennum & Sjol, 1992).

In the general adult population 59% report snoring (Hiestand et al., 2006) and in other studies 25 - 28% and 44 - 46% of women and men, respectively, report habitual snoring (Duran et al., 2001; Young et al., 1993). These two population-based studies demonstrated an independent association between snoring and OSA with the odds ratios for sleep apnea that range from 2.87 to 4.72 with habitual snoring after adjusting for age, gender, race, BMI, neck girth, and waist to hip ratio in a multicenter American population (Young, Shahar et al., 2002), and age and gender in a Spanish population (Duran et al., 2001), respectively. Often those with OSA report such severe, disruptive snoring that it can be considered socially isolating even within a marital relationship (Cartwright & Knight, 1987). Thus, snoring is a common and sometimes isolating symptom of OSA. However, it is neither a necessary or sufficient condition for the presence of OSA and is conversely also quite common in the general population without OSA.

Excessive sleepiness is the most common daytime symptom among those with OSA (Engleman & Douglas, 2004). It too is a relatively common symptom in the general population with 26% reporting that they wake up feeling tired or fatigued (Hiestand et al., 2006). As a subjective symptom, sleepiness is better characterized and often measured with a descriptive tool such as the Epworth Sleepiness Scale (ESS) (Johns, 1991; Kirsch & Chervin, 2007). When sleepiness was originally measured among those with OSA using the ESS the score correlated with the severity of OSA based on RDI (Johns, 1991). This relationship between OSA severity and sleepiness as defined by the ESS was also demonstrated in a large population-based study, the Sleep Heart Health Study (Gottlieb et al., 1999). However, it is important to note that nearly two-thirds of those with severe OSA (AHI>30) do not meet the ESS criteria for excessive daytime sleepiness (ESS score>10) (Gottlieb et al., 1999).

Obesity has long been associated with OSA as illustrated by the prototypical case of sleep apnea, Joe, the Fat Boy, from Charles Dickens (Conti et al., 2006). Of the studies reviewed in Table 1 above, all 20 of the studies that considered obesity as a covariate for either presence or severity of OSA found an association. The remaining studies (Gislason et al., 1988; Lavie, 1983; Roehrs, Kapke, Roth, & Breslau, 2006) did not present an analysis of obesity as an OSA covariate. Some reviewers (Young, Peppard et al., 2002) have suggested that there is "little controversy that the associations seen in observational studies represent a causal role of excess weight in OSA" (p. 1228).

In the multicenter Sleep Heart Health Study a one standard deviation difference (5.3 kg/m^2) in Body Mass Index (BMI) increased the odds of OSA by about 55% when age, gender, race, and snoring were held constant (Young, Shahar et al., 2002). In

addition, a longitudinal weight increase of 10% is associated with a 32% increase in OSA severity as measured by the apnea-hypopnea index, whereas a 10% reduction in weight reduces OSA severity by 26% (Peppard, Young, Palta, Dempsey, & Skatrud, 2000). Thus, though difficult to achieve, weight loss can be effective in treating OSA (Veasey et al., 2006).

Male gender has been considered an OSA risk factor. OSA is generally two to three times more common among men than women (Strohl & Redline, 1996). In the two large population based studies of OSA prevalence male to female gender ratios ranged from 1.67:1 (Baldwin et al., 2001) to 3.7:1 (Young et al., 1993) depending on the severity criteria used to define OSA. Among sleep clinic populations the male predominance was much greater with reviewers citing ratios of 5-8:1 (Jordan & McEvoy, 2003) to as high as 90:1 (Strohl & Redline, 1996). This suggests that men are more likely to be referred for sleep clinic evaluation possibly because they have more severe disease and more classic symptoms (Jordan & McEvoy, 2003; Shepertycky, Banno, & Kryger, 2005; Strohl & Redline, 1996).

OSA Clinical Diagnosis

Historically polysomnography (PSG) has been the recommended technique for the clinical diagnosis of OSA (Chesson et al., 1997; Schlosshan & Elliott, 2004; P. L. Smith et al., 1994). This technique involves the placement of multiple electrodes, probes, and belts to monitor neurological, respiratory, cardiovascular, and other physiologic parameters during sleep. It is typically carried out in a hospital-like setting with a sleep technician present to supervise and monitor the recording of these multiple parameters (Berry, Geyer, & Carney, 2005; Bloch, 1997; Chesson et al., 1997; Schlosshan & Elliott,

2004). Thereafter the PSG recording is interpreted by a physician to formulate an interpretation and clinical diagnosis.

Accepted OSA diagnostic criteria (Flemons et al., 1999) include both subjective symptoms and objectively measured obstructive events during sleep. Obstructive sleep events occurring at a rate of least 15 per hour of sleep (AHI $\geq$ 15), regardless of subjective symptoms, meets these criteria for OSA, as does an AHI of five or more, but less that 15, with subjective symptoms such as excessive daytime sleepiness, choking or recurrent sleep awakenings, unrefreshing sleep, daytime fatigue or impaired concentration. OSA severity is graded based on AHI with 5 – 15 classified as mild whereas 15 – 30, and >30 being considered moderate and severe, respectively.

Though full, attended polysomnography is the primary OSA diagnostic method, other unattended testing methods with fewer recorded physiologic parameters (Collop et al., 2007; Ghegan, Angelos, Stonebraker, & Gillespie, 2006; Littner, 2005) and alternative clinical diagnostic strategies have been considered (Brietzke, Katz, & Roberson, 2004; Mulgrew, Fox, Ayas, & Ryan, 2007; Senn, Brack, Russi, & Bloch, 2006). The unattended diagnostic devices and methods have been classified as Levels II to IV based on the number and type of physiologic sleep parameters monitored during the study; full, attended PSG is then designated a Level I study (Littner, 2005). Clinical guidelines developed by the American Academy of Sleep Medicine recommend that these unattended techniques only be used in the context of a comprehensive patient evaluation system in populations where the sensitivity and specificity of the method is known (Collop et al., 2007).

Among the other diagnostic strategies has been a clinical medical history and physical exam. This strategy has proven to be ineffective with a low sensitivity and specificity even when performed by expert clinicians (Brietzke et al., 2004; Viner, Szalai, & Hoffstein, 1991). More recently a diagnostic algorithm combined with a therapeutic trial of CPAP and follow up overnight oximetry (a Level IV unattended monitoring) was shown to be as effective as full PSG in making the diagnosis in a population with high OSA prevalence. The study suggested that with this strategy treatment adherence was improved compared to standard methods (Mulgrew et al., 2007).

Recently a coverage determination by the Centers for Medicare and Medicaid may allow reimbursement OSA treatment with CPAP when the OSA has been diagnosed using Level II to IV unattended diagnostic methods. (Phurrough, Jacques, Spencer, Stiller, & Brechner, 2008) Historically CPAP was reimbursed only when OSA was diagnosed using full PSG. Thus, it is possible that the clinical diagnosis of OSA will in the future be more commonly made in some settings using unattended diagnostic methods. Thus, the assessment of the prevalence of clinically recognized OSA in the first decade of the 21st century would be a timely and useful benchmark for comparison to the previous assessments in the 1990s (Kapur et al., 2002; Young, Evans et al., 1997) prior to potential change in diagnostic methods used for the future.

OSA Treatment

There have been multiple treatment modalities employed for OSA. Weight loss by dietary restriction has been demonstrated to reduce the severity of OSA and associated hypertension (Kansanen et al., 1998; Suratt, McTier, Findely, Pohl, & Wilhoit, 1992). However, the maintenance of weight loss is difficult in the long term, and OSA does

recur even in those that are able to maintain a reduced weight (Sampol et al., 1998). Though more than 20 different drugs have been tested for the treatment of OSA, in clinical trials none have been proven effective (I. Smith, Lasserson, & Wright, 2006).

Several surgical and mechanical treatments have, however, been demonstrated to be effective. A surgical tracheostomy which places a permanent opening in the airway below the area of airway obstruction in OSA was among the first treatments shown to be effective in the long-term (Guilleminault et al., 1981). Other surgical procedures used for OSA involve modifications to both soft tissue and boney structures (Colin & Duval, 2005). A 1996 systematic review of the success of surgical OSA treatment found success rates no higher than 50% (Sher, Schechtman, & Piccirillo, 1996). Subsequently the surgical approaches have used staging systems (Friedman, Ibrahim, & Joseph, 2004; Li, Powell, Riley, Troell, & Guilleminault, 1999) that attempt to more directly tailor the surgical procedure(s) to the OSA patient's specific anatomy. With such staging there has been improved success rates in the 70 – 80% range for some OSA anatomical types (Friedman & Schalch, 2007).

Oral and dental appliances are devices that move the mandible anteriorly or retain protrusion of the tongue during sleep (Chan, Lee, & Cistulli, 2007). There is some variability in the definition of treatment success in the oral appliance literature. However, for mild to moderate OSA there is overall a 52% success rate (Ferguson, Cartwright, Rogers, & Schmidt-Nowara, 2006). Controlled trials have demonstrated that these appliances are generally inferior to continuous positive airway pressure treatment (Lim, Lasserson, Fleetham, & Wright, 2006).

Continuous positive airway pressure (CPAP) is considered to be first-line therapy for those with moderate to severe OSA, especially those that have symptomatic daytime sleepiness (Giles et al., 2006; Kushida et al., 2006). CPAP devices use airflow generated by a fan and applied to the patient's airway by way of tubing and a nasal or oronasal mask to maintain the patency of the airway during sleep. Thus, CPAP functionally represents a pneumatic splint that prevents OSA-related airway obstruction (Hirshkowitz & Sharafkhaneh, 2005).

There have been two recent comprehensive literature reviews (Gay et al., 2006; Weaver & Chasens, 2007) of studies of CPAP therapy efficacy for OSA in adults. Combined these two reviews considered a total of 34 published studies that met the quality criteria regarding relevance and study design for the respective review. Of these studies a wide variety of study end points were used including AHI reduction, improved sleep architecture, reduction in daytime sleepiness and other OSA-related symptoms, improved neurobehavioral symptoms, functional status, quality of life, blood pressure, cardiac function, coagulation factors, cholesterol, and nocturia (Gay et al., 2006; Weaver & Chasens, 2007).

Collectively in these two reviews (Gay et al., 2006; Weaver & Chasens, 2007) a total of 28 of the 34 papers demonstrated some beneficial effect for CPAP with OSA with respect to at least one of the endpoints studied. These studies included variable study designs, disease severities, ages, treatment, and endpoint definitions. Endpoints involving daytime sleepiness, snoring, gasping, cognitive processing, memory, executive function, motor speed, and nonverbal learning variably demonstrated improvement in one or more studies. When studied in populations with moderate and severe OSA (defined as an AHI

greater than 15 with daytime sleepiness) the following endpoints demonstrated more consistent improvement with CPAP: AHI, sleep architecture, blood pressure, cardiac contractility, stroke volume, vascular resistance, and platelet coagulability (Gay et al., 2006; Weaver & Chasens, 2007).

Gay and colleagues (2006) found that eight studies that had reported no improvement for the endpoints considered did not report a power analysis estimating the probability of Type II error for these negative results. Of the additional six negative studies (Barbe et al., 2001; Henke, Grady, & Kuna, 2001; Kajaste, Brander, Telakivi, Partinen, & Mustajoki, 2004; Robinson, Pepperell, Segal, Davies, & Stradling, 2004; Robinson, Smith, Langford, Davies, & Stradling, 2006) included in the later review (Weaver & Chasens, 2007) only one reported a power analysis (Robinson et al., 2006).

That study (Robinson et al., 2006) used a power analysis based on detection of a 5 mm of Hg blood pressure reduction with CPAP. However, from the cardiovascular literature, a meta-analysis of 29 studies involving more than 150,000 patients a population mean blood pressure reduction as small as two mm of Hg produced statistically significant reduction in risk for stroke and cardiovascular disease (Turnbull, 2003). So the study by Robinson and colleagues (2006) may not have been sufficiently powered to detect the smaller blood pressure changes that other studies have shown to be associated with cardiovascular risk reduction. Therefore, these 14 negative studies generally may not have been of sufficient size to avoid Type II errors in evaluating physiologic endpoints.

Indeed two subsequent meta-analyses specific to the effect of CPAP on blood pressure (BP) in randomized controlled clinical trials, indicate that mean BP is reduced

about 1.7 mm Hg based on 572 participants (Haentjens et al., 2007) whereas systolic BP is reduced about 2.5 mm Hg based on 818 participants (Bazzano, Khan, Reynolds, & He, 2007). An additional small study (Hui et al., 2006) not included in these meta-analyses demonstrated a reduction in 24 hour mean BP of 3.8 mm Hg. Thus, the identification and treatment of those with OSA is associated with a population BP reduction of a magnitude that has produced a reduction of stroke and cardiovascular risk in pharmacologic treatment studies.

The benefits of CPAP treatment in those with moderate to severe OSA including daytime symptoms has been well established and accepted (Gay et al., 2006; Weaver & Chasens, 2007) even by those taking a conservative position regarding CPAP treatment in OSA (Montserrat, Barbe, & Rodenstein, 2002; Wright & Sheldon, 2000). Whether to treat mild to moderate OSA, and those without daytime symptoms has been much more controversial having been the topic of two point-counterpoint pairs of editorials in the sleep literature (Davies & Stradling, 2000; Levy, Pepin, & McNicholas, 2002; Montserrat et al., 2002; Wright & Sheldon, 2000).

A recent meta-regression of randomized controlled trials of CPAP demonstrated that, across the spectrum of OSA severity, the reduction in blood pressure with CPAP though larger with a higher AHI, approaches zero with a pre-treatment AHI between 10 and 20 (Haentjens et al., 2007, Figure 3A, p. 762). In reviewing randomized studies of CPAP treatment restricted to those with mild to moderate disease Gay and colleagues (2006) report that CPAP did reduce AHI, did not improve objective sleepiness or blood pressure, and had mixed results for subjective sleepiness, and quality of life. However, a later meta-analysis (Marshall et al., 2006) that included one additional study (Marshall,

Neill, Campbell, & Sheppard, 2005) not available to Gay and colleagues (2006) that was able to demonstrate collectively a statistically significant improvement in both subjective sleepiness by the Epworth Sleepiness Scale, and objectively with the Maintenance of Wakefulness Test. In this analysis (Marshall et al., 2006) a significant improvement with the Multiple Sleep Latency Test was not found. Thus, though the treatment effect is smaller, and thus more difficult to detect without larger samples or pooled data, there does appear to some benefit to CPAP treatment of mild to moderate OSA.

Research regarding efficacy of CPAP has been challenging in the selection of an adequate control for the CPAP treatment (Babar & Quan, 2003; Hein, 2002; Wright, Johns, Watt, Melville, & Sheldon, 1997). In the review by Weaver and Chasens (2006) eight of the 26 controlled trials reviewed used a placebo tablet, and four used conservative measures such as a low calorie diet and behavioral therapy, whereas 12 studies used subtherapeutic or sham CPAP as the control. Subtherapeutic or sham CPAP involves the participants' use of a CPAP machine that is either set to provide a pressure so low that it should be ineffective, or with a CPAP system modified to prevent it from delivering a therapeutic pressure (Farre et al., 1999). Not surprisingly there is evidence from research with acupuncture that there is a differential placebo effect between sham devices and tablet placebos (Kaptchuk et al., 2006). There has also been controversy regarding the ethics of the deception associated with the use of sham CPAP and other placebos in CPAP research (Karlawish & Pack, 2001). Thus, it seems there is no ideal placebo control for the evaluation of CPAP efficacy, and this research must be interpreted in light of these limitations.

Overall, CPAP treatment effects have been most consistently beneficial in those with moderate to severe disease with symptoms of daytime sleepiness (Gay et al., 2006; Weaver & Chasens, 2007). However, as described in the analysis of Table 1 above there is evidence that those with mild sleep disordered breathing even without daytime sleepiness are also at increased risk of hypertension, a known cardiovascular risk factor (E. O. Bixler et al., 2000; Nieto et al., 2000; Young et al., 1993; Young, Peppard et al., 1997; Young, Peppard et al., 2002). Because the evidence from controlled trials, albeit some underpowered studies, has not demonstrated a clear benefit from CPAP treatment in mild OSA without daytime symptoms, treatment with CPAP in this population remains controversial (Gay et al., 2006; Hedner & Grote, 2001; Levy et al., 2002; Weaver et al., 2007).

The ability to adhere to prescribed CPAP therapy among those with OSA has been limited and variable. A classic study (Kribbs et al., 1993) had demonstrated that only 46% were able maintain use of CPAP at ≥4 hours per night. A recent review of the CPAP adherence literature (Weaver & Grunstein, 2008) using a standard of at least 4 hours of CPAP application per night, found a wide range of adherence from 17 – 71%. This review suggested that OSA disease severity, as measured by AHI and level of night time hypoxia, were only weak predictors of adherence. Technological CPAP innovations such various mask interfaces, heated humidification, and automatic pressure titration or bilevel positive airway pressure devices have been shown to only minimally enhance adherence (Haniffa, Lasserson, & Smith, 2004; Weaver & Grunstein, 2008) despite the fact that many of these innovations have often been marketed for improved adherence (Weaver & Grunstein, 2008). Other adherence enhancement interventions involving

cognitive behavioral therapy have demonstrated an increase in the average number of hours used nightly by 1.5 (Hoy, Vennelle, Kingshott, Engleman, & Douglas, 1999) to 2.9 hours (Richards et al., 2007). Thus, it is likely that clinical optimization of adherence will require a multidimensional program involving device technical support and, more importantly, cognitive behavioral support (Engleman & Wild, 2003).

Limited Clinical Recognition of OSA

Historically most people with OSA have been clinically undiagnosed. Among the earliest reports was a published letter from British physicians (Apps, Gillon, & Stradling, 1983) suggesting that the disorder was under diagnosed in the United Kingdom relative to America. Then, based on hospital discharge diagnostic code data from 1985 to 1987, it was reported that only 36 from the database of about ten million discharges were found to reference OSA (Dement, 1993; Strohl & Redline, 1996). If the OSA population prevalence in this mixed gender population is postulated to be about 3% based on a population based study initiated in 1988 (Young et al., 1993) and making the assumption of an approximately equal gender mix among these hospital discharges, there would have been about 300,000 participants with OSA in this cohort. Thus, the 36 diagnostic references to OSA among these discharge diagnoses might suggest a very low prevalence of clinical diagnosis at about 0.012%.

Given that OSA is generally managed in the outpatient setting there is some weakness in assessing clinical OSA recognition from such an inpatient database. However, in a diagnostic review of outpatient charts for ten northern California primary care clinics in 1991 there was no mention of an OSA diagnosis for any of the participants in the nonpopulation-based sample (Strohl & Redline, 1996). Thus, though recognizing

the weaknesses of these early assessments of OSA clinical recognition, it appears that as recently as 1991 OSA was very infrequently identified by the clinical care system.

Population-based studies of OSA clinical recognition

There have been two systematic population-based studies conducted using data collected in the 1990s that have assessed the clinical recognition of OSA (Kapur et al., 2002; Young, Evans et al., 1997). The earlier of these two studies (Young, Evans et al., 1997) was based on data from the Wisconsin Sleep Cohort (Young et al., 1993) and identified participants clinically diagnosed with OSA based on their indication on a mailed survey that they had been told by a physician that they had sleep apnea. From the 4925 who responded to the survey, positive responses were received from 49 participants. Telephone follow up of those respondents showed that only 16 had actually been clinically diagnosed whereas nearly all of the others had only personally suspected OSA but had never been clinically evaluated. These 16 participants represented 15.4% of those ultimately identified with moderate to severe OSA, and 6.5% of those identified with the broader spectrum of mild to severe OSA based on the study's screening and polysomnography methods. When stratified by gender it was estimated that only 7% and 18% of women and men, respectively, with moderate to severe OSA, and 2% and 10%, respectively, with mild to severe OSA had been diagnosed. A demographic comparison of those diagnosed clinically and those identified by study screening showed that only male gender and age statistically predicted clinical diagnosis. In addition, there was a trend toward a history of hypertension or cardiovascular disease and higher income among those diagnosed clinically (Young, Evans et al., 1997).

This study (Young, Evans et al., 1997) has a number of strengths including its population-based sample, two stage screening with both high risk and low risk participants undergoing PSG, diagnosis of OSA based on in laboratory rather than in home PSG, and confirmation of survey reports of physician OSA diagnosis. Among the weaknesses are the truncated age range that involved no patients over age 60, the fact that only positive responses to the physician diagnosis survey question were confirmed, and the lack of medical record verification of physician diagnoses. Overall, within these limitations the study appears well done.

The later study (Kapur et al., 2002) was based on data from the multicenter Sleep Heart Health Study (Quan et al., 1997) which included a total of nearly 16,000 participants. Those clinically diagnosed with OSA were identified based on their positive response to question "Have you ever been told by a physician that you have sleep apnea?" (Kapur et al.,2002, p. 50). The study's screening for prevalent OSA was based on participants' response to survey questions regarding frequency of snoring and excessive daytime sleepiness. Participants that reported snoring three or more nights per week and feeling excessively sleepy more than five days per month were identified as being "consistent with a higher probability" (Kapur et al.,2002, p. 50) of OSA, particularly those with moderate to severe OSA.

By survey responses 253 participants reported having a physician diagnosis of OSA with 90 of these under treatment whereas 650 participants met the proxy criteria for OSA. Of the 650 participants meeting the OSA proxy criteria, 54 or 8.3% reported physician diagnosis. Demographic analysis of these participant groups demonstrated that the following factors were statistically more common among those at risk for moderate to

severe OSA who reported being diagnosed and treated for OSA: male gender, body mass index, hypertension, lower HDl cholesterol, and being a college graduate. In a logistic regression model using these factors only male gender and body mass index remained statistically significant.

In their analysis of these results Kapur and colleagues (2002) noted that OSA prevalence using this proxy criteria was 4.1% which was comparable to that in a previous population based sample (Young et al., 1993). However, among the 10 sites involved in the study the prevalence varied from 1.55% to 7.23% with prevalence of physician diagnosed, and physician diagnosed and treated OSA showing comparable inter-site variation albeit at much lower prevalence rates. The authors also noted that some in the physician diagnosed, and physician diagnosed and treated groups did not meet the study's OSA proxy criteria. These OSA proxy criteria were not validated as a part of the study nor were they specifically validated as OSA proxy criteria in any of the references cited in support of these criteria (Bradley et al., 1998; Newman et al., 2001; Strohl & Redline, 1996). Rather, these references identified these criteria as important risk factors, among others, for OSA. Therefore the sensitivity, specificity, and other performance characteristics of the proxy criteria used for OSA in the study are unknown.

From the nearly 16,000 participants in the study (Kapur et al., 2002) some 6400 were elsewhere reported to have undergone in home polysomnography (Shahar et al., 2001). Thus, an opportunity existed for validating the proxy criteria in the same sample, or alternatively, the study could have been performed using home polysomnography as the basis for OSA diagnosis. The study's methods (Kapur et al., 2002) also did not attempt to verify survey respondents' reports of physician OSA diagnosis and treatment,

though it did acknowledge the resulting possibility of misclassification. Based on the earlier study (Young, Evans et al., 1997) where only 33% of those reporting a physician diagnosis of OSA were confirmed, it is unfortunate that this study did not attempt to validate, even a portion of these positive responses.

In comparing these two studies (Kapur et al., 2002; Young, Evans et al., 1997), the point prevalences reported for clinically recognized moderate to severe OSA are generally compatible with Kapur and colleagues (2002) having reported 8.3% whereas Young and colleagues (1997) had reported 7% and 18% in women and men, respectively, and 15.4% overall. Though the larger sample size represents a strength of the Kapur (2002) study, with the lack of validation for the study's method of identifying OSA, and lack of confirmation for any of the participant reported physician OSA diagnoses, it seems that this study has less credibility relative to the early study (Young, Evans et al., 1997).

There have been two more recent nonpopulation-based studies that analyzed OSA clinical recognition (Brown et al., 2009; Warmouth et al., 2008). The first, presented in abstract form (Warmouth et al., 2008), involved a sample of patients undergoing preoperative assessment for surgery that found 159 participants from a sample of 2614 had been previously diagnosed with OSA. Of the remaining participants that completed OSA screening using the BQ (n = 2316) there were 671 (29%) who were identified as high risk for OSA. A total of 830 participants were identified with OSA or at high risk for OSA by either clinical report or the BQ, respectively. Thus, the prevalence of clinical recognition for this group of 830 participants from a nonpopulation-based sample was 19.2%.

The second study (Brown et al., 2009) conducted as an online survey of professional orchestra players identified 348 (31%) participants as being high-risk for OSA based on the BQ in a mixed gender sample. Of these, 66, representing 19.1% of those with BQ identified OSA, had been clinically recognized based on participant self-report.

The prevalence of clinically recognized OSA reported by these two studies is similar to that reported in the population-based sample by Young and colleagues (1997) for men, but higher than that reported for women by Young and colleagues (1997) and in a gender mixed population by Kapur (2002).

In summary, in population based studies there is very limited clinical recognition of moderate to severe OSA with a range from 7-18% for women and men, respectively, with the most recent credible study having been conducted in the mid-1990s.

Analysis of the OSA under-recognition problem

A report from the National Commission on Sleep Disorders Research (Dement, 1993) suggested that some 70 million Americans suffered from a spectrum of sleep disorders including OSA that had consequences including "reduced productivity, lowered cognitive performance, increased likelihood of accidents, higher morbidity and mortality risk, and decreased quality of life" (p. vi). The Commission estimated that in 1990 the associated direct sleep-related costs totaled more than $15.9 billion with billions of additional indirect costs related to accidents and diminished productivity. The report's analysis (Dement, 1993) suggested that general public ignorance and a lack of health professional education regarding sleep-related disease were among the factors

responsible for the failure of American society "to recognize and attend effectively to sleep-related issues" (p. vi).

Limited physician awareness of OSA has long been identified as one of the explanations for the limited clinical recognition of OSA. Among the earliest published reports of limited physician awareness of OSA came from a national sample of the American Geriatrics Society (Haponik, 1992). This telephone survey of 45 physicians conducted in 1990 demonstrated that, though 73% of the physicians surveyed believed sleep problems were an important part of their practice, none identified sleep apnea an important cause of their patients' sleep disturbances. A decade earlier a study of medical school curricula had demonstrated that 93% of American medical schools provided no instruction in sleep disorders (Orr, Stahl, Dement, & Reddington, 1980), probably at least in part, accounting for this lack of awareness.

By 1988 informal surveys suggested increased medical school instruction and a curricular outline was provided to guide further developments (Dement et al., 1988). The increase in sleep curricula was documented with the 1993 publication of a survey of 126 medical schools (R. C. Rosen, Rosekind, Rosevear, Cole, & Dement, 1993). This survey demonstrated an average of about two hours of total instructional time in the preclinical and clinical curricula, but 29.4% of medical schools continued to have no structured sleep and sleep disorders curriculum.

A systematic study of outpatient clinical diagnoses from a nationally representative practice sample demonstrated a 12-fold increase in the number of OSA diagnoses made over the nine year time period from 1990 to 1998 (Namen et al., 2002). This increase occurred while the diagnosis of common disorders such as hypertension

and upper respiratory tract infection, and less common sleep disorders such as narcolepsy and parasomnias, all remained essentially constant. The sampling frame of this study did not allow assessment of the prevalence of clinically recognized OSA. The study found over this time period a statistically significant correlation of increasing OSA diagnoses with increases in the number of OSA publications in the medical literature and the number of accredited diagnostic sleep laboratories. Namen and colleagues (2002) concluded that their observations suggested "a positive response on the part of health-care providers to the prevalence and morbidity" (p. 1747) of OSA.

Two reports have assessed physician awareness of sleep disorders. The first conducted in late 1999 and early 2000 reported on a survey and knowledge assessment of primary care physicians in northeastern Ohio (Papp et al., 2002). Ninety per cent of respondents agreed that OSA was potentially life-threatening, and 84% indicated it was a common problem. However, in the 33 item multiple choice sleep knowledge assessment, the mean number of correct items was 12. This may suggest an increased awareness of OSA compared to that demonstrated by Haponik in 1992, though Papp and colleagues (2002) concluded that there was "a low rate of expertise" (p. 105).

The second study (Reuveni et al., 2004) was conducted in Israel and included no graduates of medical schools in the United States. This study used a very different method incorporating a standardized patient into the practices of randomly selected primary care physicians consenting to the study. The standardized patients reported suffering from "fatigue, reduction in work efficiency and a general reduction in mental function" (p. 1524) and reported having recently been involved in an automobile crash (Reuveni et al., 2004). The physician participants were then allowed to ask as many

questions as they felt appropriate. Of the five questions identified by sleep experts as important questions for this patient presentation only 10% of the primary care physician sample asked three or more, 30% only asked one while 50% of the physicians failed to ask any of the identified questions. In knowledge assessment questions following the standardized patient interview, 87% recognized that polysomnography was needed in the diagnosis of OSA, and 90% recognized that CPAP was useful in its treatment (Reuveni et al., 2004). Thus, though these physicians clinical acumen for recognizing probable OSA in their practice was quite limited, a large majority did have a basic knowledge of strategies for OSA diagnosis and treatment.

Other studies have also demonstrated that instructional interventions for physician can enhance their clinical recognition of OSA. In a study of primary care physicians and medical interns, among those that had received training in sleep disorders 82% obtained a sleep history in standardized patient encounters whereas only 13% of untrained interns and none of the primary care physicians obtained this history (Haponik et al., 1996).

A more comprehensive intervention in Walla Walla, Washington involved the education of physicians, along with education of the general public and the development of a local sleep testing laboratory (Ball et al., 1997). This intervention let to an increase in evaluation by PSG from 0.27% to 2.1% of adult patients. Of the 360 patients that underwent PSG in the project, 276 (77%) were found to have OSA. Of the 214 patients for whom CPAP was prescribed and whose CPAP usage status could be assessed, only 22% had returned their CPAP machine one to three years after testing. The authors (Ball et al., 1997) concluded that community physicians can identify and care for a much larger portion of those with OSA if provided education and support.

Finally, an educational intervention for medical residents and attending physicians regarding sleep disorders that extended over a four year period demonstrated an increase in the annual referral rate for PSG from 0.06% to 0.21% of active patients (Zozula et al., 2005). However, the prevalence of clinical recognition only increased from 0.11% to 0.26% of active patients. Among the factors that were identified as barriers to clinical recognition in the study were the fact that 48% of those referred for PSG failed to complete the study, and that 16% of the PSGs completed did not have a report available to the patients' physicians thus limiting the opportunity for implementation of treatment.

It seems clear that physician awareness of sleep disorders such as OSA has contributed to the lack of clinical recognition of OSA, and that instruction regarding sleep disorders does increase the rate of clinical recognition by physicians.

Patient access to sleep laboratories and sleep specialists has also been identified as a factor contributing to the low rate of clinical recognition of OSA (Flemons et al., 2004; Morgenthaler et al., 2006). The first of these reports (Flemons et al., 2004) presents an international analysis of the availability of sleep laboratories and PSG in the United States, United Kingdom, Belgium, Canada, and Australia. That analysis found waiting times for polysomnography ranged from two to sixty months, and that the number of PSGs performed relative to the population varied five-fold across these countries. The authors (Flemons et al., 2004) predict that in order to diagnose and manage currently undiagnosed OSA (based on Young, Evans et al., 1997) over a 10-year period based on the prevalence of only moderate to severe OSA (based on Young et al., 1993) an additional 555 PSGs per 100,000 population would be required each year. In addition, with the 600 PSGs per 100,000 required for new, incident cases, and if, on average, 50%

of diagnostic PSGs are positive, the authors project the need for a total of 2310 PSGs per 100,000. In 2003 this demand exceeded the capacity in the United States by a factor of 5.4 and in the United Kingdom by a factor of 54, and fails to account for PSGs needed for any other type of sleep disorder. Thus, despite a 12-fold increase in the number of OSA diagnoses made in the 1990s, and a doubling of the number of accredited sleep laboratories (Namen et al., 2002) Flemons and colleagues (2004) projected a need to further increase the number of PSGs performed by more than 5-fold.

An analysis at one large institution's sleep center demonstrated that sleep referrals from within the institution exceeded capacity by nearly 100% (Morgenthaler et al., 2006). In response, that institution developed an alternative evaluation method reducing the physician time spend by 50% in order to increase capacity and found that patient outcomes and satisfaction were maintained relative to standard evaluation methods. Subsequently this alternative process was adopted as the standard at the sleep center (Morgenthaler et al., 2006).

In studies of PSG utilization a wide variability has been found across both the United States and Australia in the number of PSGs performed for the population (Marshall et al., 2007; Tachibana, Ayas, & White, 2005). The American study (Tachibana et al., 2005), based on a survey of accredited sleep laboratories found that there were on average about 427 PSGs performed per 100,000 population on an annual basis. However, by state this rate varied by nearly 10-fold from 121 in Colorado, to 1161 in Maryland. Thus, it would appear that availability of PSG varies substantially across the United States. A similar variability in the PSGs performed for the population has been

noted in Australia where the overall number of PSGs per 100,000 population has increased by about 150% from 1995 to 2004 (Marshall et al., 2007).

In addition to increasing access to sleep laboratories and specialists, commentators (Banno & Kryger, 2004; Pack, 2004; Tarasiuk & Reuveni, 2004) have proposed a number of other strategies to increase access to OSA diagnosis including the use of home PSG, overnight oximetry recordings, and symptom scoring algorithms. Two recent trials have initiated CPAP treatment without prior diagnostic PSG (Mulgrew et al., 2007; Senn et al., 2006). The first study used clinical improvement with CPAP as a proxy diagnosis of OSA among participants referred for evaluation of possible OSA (Senn et al., 2006). In this study response to CPAP at 2 weeks had positive and negative predictive values for PSG confirmed OSA of 97% and 78%, respectively. Of those with OSA identified by CPAP response, 94% then had a successful and sustained response to CPAP treatment at four months (Senn et al., 2006).

In the second study, a randomized clinical trial, CPAP treatment was initiated for presumed OSA among those with a pre-treatment probability of OSA of at least 95% and compared to traditional diagnostic PSG followed by CPAP treatment (Mulgrew et al., 2007). The study demonstrated similar CPAP effectiveness with and without diagnostic PSG, and improved CPAP adherence among those treated without initial PSG (Mulgrew et al., 2007).

Access to PSG has been a factor limiting the clinical recognition of OSA and probably continues to remain a limitation. However, in the past 15 years there has been an increase in the access to PSG and there are under development a number of alternative

diagnostic and treatment strategies for OSA that are less reliant on PSG for diagnosis of OSA.

Because laboratory PSGs are expensive and somewhat intrusive, the very nature of the diagnostic evaluation has been a factor identified as contributing to the limited prevalence of clinical recognition of OSA (Colten & Altevogt, 2006). The fact that one must spend one or more nights away from home in order to be evaluated in the sleep laboratory is particularly problematic for those with responsibility for the care of family members (Colten & Altevogt, 2006). In addition, there is the suggestion from one qualitative study that the challenges associated with the process of diagnosis ultimately had a negative impact on patients' interest and ability to adhere to therapy following diagnosis (van de Mortel et al., 2000).

In summary the following factors have been identified as contributing to the limited prevalence of clinical recognition of OSA: (a) limited OSA awareness by physicians, (b) limited access to sleep laboratories and specialists, and (c) the expensive and intrusive nature of laboratory-based PSG. There is evidence that to some extent there have been improvements with regard to several of these factors with enhanced physician education related to OSA, increased access to sleep studies laboratories, and the development of diagnostic technologies less dependent on PSG. Thus, it is reasonable to hypothesize that the prevalence of clinically recognized OSA has increased since the 1990s.

The Berlin Questionnaire

The Berlin Questionnaire is an eleven item instrument that was developed in 1996 by consensus at the Conference on Sleep in Primary Care in Berlin, Germany (Netzer et

al., 1999). The questions were chosen to identify characteristics that placed participants at high risk for OSA in the areas of snoring, daytime sleepiness, hypertension, and obesity. The instrument's scoring algorithm places participants in one of two categories, high or low risk, for OSA. The instrument was initially validated in consecutive patients seen for any reason in the practices of five internal medicine physicians in the Cleveland, Ohio area (Netzer et al., 1999).

Of the 1008 BQs distributed for this initial report 744 were completed and included in that analysis. The validation study invited the 75 participants placed by the instrument at high risk, and the 65 participants placed at low risk, to under go in-home, unattended PSG. Participants for PSG were selected from alphabetically ordered lists and were visited in their homes for instruction regarding use of the PSG device. Ultimately 100 participants completed PSG with scorable studies including 69 of the 75 from the high risk group and 31 of 65 in the low risk group. The PSGs were scored by a single researcher who was blinded to the results of the questionnaire (Netzer et al., 1999).

The initial publication of the validation study reported sensitivities for OSA based on RDI criteria of >5, >15, and >30 as being 0.86, 0.54, and 0.17, respectively. Specificities at these same RDI levels were reported as 0.77, 0.97, and 0.97, respectively. The positive predictive value (PPV) for OSA at an RDI >5 was reported as 0.89. However, a subsequent letter to the editor raised questions about these calculations (Strauss & Browner, 2000). Based on the published validation data from Netzer and colleagues' original paper (1999) sensitivities, specificities, positive and negative predictive values (PPV and NPV) are recalculated using standard methods (Weiss, 2008) in Table 2.

Table 2

BQ Performance Measures Calculated From Data Published in Netzer, et al (1999)

RDI criterion for OSA	BQ Result	OSA positive by PSG	OSA negative by PSG	Total	BQ Performance Measures			
					Sensi-tivity	Speci-ficity	PPV	NPV
RDI > 5	High Risk	59	10	69	59/66 = 0.894	24/34 = 0.706	59/69 = 0.855	24/31 = 0.774
	Low Risk	7	24	31				
	Total	66	34	100				
RDI > 15	High Risk	37	32	69	37/38 = 0.974	30/62 = 0.484	37/69 = 0.536	30/31 = 0.968
	Low Risk	1	30	31				
	Total	38	62	100				
RDI > 30	High Risk	12	57	69	12/13 = 0.923	30/87 = 0.345	12/69 = 0.174	30/31 = 0.968
	Low Risk	1	30	31				
	Total	13	87	100				

Thus, based on this re-calculation of these performance measures for OSA with an RDI severity of greater than five and including no daytime sleepiness requirement the BQ demonstrated a sensitivity of 89.4%, specificity of 70.6%, positive predictive value of 85.5%, and a negative predictive value of 77.4%. Note that this level of severity is similar to that which rather consistently demonstrated a population prevalence of 19 – 25% for adult men in the analysis of Table 1 above.

The questionnaire consists of 11 questions grouped in three categories ("Reprinting of the Berlin Questionnaire," 2000). Most of the questions are answered using a series of responses on an ordinal frequency or severity scale. Based on participants' responses to the questions in each category that category is scored as either positive or negative. If least two of the three categories are positive the participant is

considered to be at “high risk” for OSA, whereas the participant is considered to be at “low risk” if less than two categories are positive. Table 2 below enumerates the categories and items.

The initial publication (Netzer et al., 1999) of the BQ provided a general description of the scoring algorithm to be used for the questionnaire but without sufficient detail to establish a specific scoring algorithm. Subsequently the questionnaire with more detailed scoring algorithms was published (Dement & Netzer, 2000). Unfortunately there were a number of errors in this more detailed publication of the algorithm that were later corrected ("Reprinting of the Berlin Questionnaire," 2000). Probably in part because the publication of this later correction was not indexed in the journal’s table of contents, or in the medical indexes, multiple scoring methods have been described by those that subsequently used the instrument.

These scoring methods have included some deviation from that original questions used by Netzer and colleagues (1999) and scoring method as subsequently published ("Reprinting of the Berlin Questionnaire," 2000). Among the deviations are the following:

1. When the instrument was reviewed by legal counsel prior to its application in atrial fibrillation and cardiology patients (Gami et al., 2004) concern was expressed regarding the vicarious liability associated with documenting that participants nodded off while driving (A.S. Gami, personal communication, July 17, 2007). Thus, items 8 and 9 (Table 3) regarding drowsy driving were not included in the questionnaire used in this study. Similarly in another study (West, Nicoll, & Stradling, 2006) these items were excluded because the item

appeared to be answered inaccurately in pilot studies, and was a deterrent to participation.

2. The original questionnaire ("Reprinting of the Berlin Questionnaire," 2000), in addition to a the binary question regarding drowsy driving (Table 3, item 8), included a follow up question regarding frequency (Table 3, item 9). At least four investigators (Chung et al., 2008; Gibbs, 2006; Leveque, Yu, Musch, Chervin, & Zacks, 2007; Singh, Drake, Roehrs, Hudgel, & Roth, 2005) have omitted this follow up question and/or its associated scoring.
3. Two investigators (Tasali, Van Cauter, & Ehrmann, 2006; Ybarra, Planas, & Pou, 2008) studying populations with near universal obesity, and a very high prevalence of hypertension excluded responses for Category 3 in their scoring.
4. One investigator, recognizing that driving a vehicle was rare in the population and culture being studied, introduced three alternative daytime sleepiness items regarding sleepiness while waiting for a doctor appointment, in line to pay a bill, and while watching television (Sharma, Vasudev et al., 2006). In addition, this investigator used a BMI cutoff of 25 rather than 30 as was described originally.
5. An additional question in Category 3 regarding a “very small jaw or a large overbite” (p. 2339) was added by one investigator (H. Singh et al., 2005).
6. One investigator (Leveque et al., 2007) scored positive responses to item 5 (Table 3) as one point rather than two as originally described.

Thus, though the basic structure of the BQ and its scoring has been consistent across its application in over 50 publications in the past decade, there have been multiple, generally subtle, variations in the questions and scoring algorithm used.

Table 3 highlights some of these BQ scoring algorithm variations relevant to the present study. Included are the original instrument and algorithm used by Netzer and colleagues (1999), the algorithm used by Gami (2004) which represented a pilot application of the instrument for the present investigation in our institution, the most recent detailed publication of a complete scoring algorithm (Gibbs, 2006), along with the algorithm used in the present study (labeled PAVD for Prevalence of Asymptomatic Ventricular Dysfunction.

Table 3

Berlin Questionnaire Items and Scoring Algorithm

Question	Responses	Points scored for the response based on identified scoring algorithm			
		Netzer	Gami	Gibbs	PAVD
Category 1: Snoring		Positive if ≥2 points scored for the following items:			
1. Do you snore?	Yes	1	0	1	1
	No/Don't know	0	0	0	0
2. If you snore, your snoring is:	Slightly louder than breathing	0	0	0	0
	As loud as talking	0	0	0	0
	Louder than talking	1	1	1	1
	Very loud, heard in adjacent rooms	1	1	1	1
3. How often do you snore?	Nearly every day	1	1	1	1
	3 to 4 nights per week	1	1	1	1
	1 to 2 nights per week	0	0	0	0
	1 to 2 nights per month	0	0	0	0
	Never or nearly never/don't know	0	0	0	0
4. Has you snoring ever bothered other people?	Yes	1	1	1	1
	No/Don't know	0	0	0	0
5. Has anyone noticed that you quit breathing during sleep?	Nearly every day	2	2	2	2
	3 to 4 times a week	2	2	2	2
	1 to 2 times a week	0	0	0	0
	1 to 2 times a month	0	0	0	0
	Never or nearly never/don't know/refused	0	0	0	0
Category 2: Daytime fatigue and sleepiness		Positive if ≥2 points scored for the following items:			
6. How often do you feel tired or fatigued after your sleep?	Nearly every day	1	1	1	1
	3 to 4 times a week	1	1	1	1
	1 to 2 times a week	0	0	0	0
	1 to 2 times a month	0	0	0	0
	Never or nearly never/don't know/refused	0	0	0	0
7. During your waketime, do you feel tired, fatigued or not up to par?	Nearly every day	1	1	1	1
	3 to 4 times a week	1	1	1	1
	1 to 2 times a week	0	0	0	0
	1 to 2 times a month	0	0	0	0
	Never or nearly never/don't know/refused	0	0	0	0
8. Have you ever nodded off or fallen asleep while driving a vehicle?	Yes	1	Not scored	1	Not scored
	No	0		0	
9. If so, how often does it occur?	Nearly every day	1			
	3 to 4 times a week	1			
	1 to 2 times a week	0	Not scored	Not scored	Not scored
	1 to 2 times a month	0			
	Never or nearly never/don't know/refused	0			

(table continues)

		Points scored for the response based on identified scoring algorithm			
Question	Responses	Netzer	Gami	Gibbs	PAVD
Category 3: Hypertension and Obesity		Positive if ≥1 point scored for the following items:			
10. Do you have a high blood pressure?	Yes	1	1	1	1
	No/Don't know	0	0	0	0
11. Body Mass Index (BMI): weight (kg)/height $(m)^2$	>30	1	1	1	1
	≤30	0	0	0	0

Overall Classification:
Participant classified as **High Risk** if two or more Categories are positive, **Low Risk** if less than two are positive.

As mentioned above, since its original publication the BQ has been used as an OSA ascertainment instrument in 53 additional research publications. As depicted in Figure 1, most of these publications have occurred in the five years from 2006 through 2010. The instrument has been used in a wide variety of settings (see Table 4), with the instrument's high risk classification having been used as a proxy for OSA in many of these publications. There has also been one published abstract that did not lead to a complete published paper that included PSG validation data (Steinel, Shaman, & Auckley, 2007) that is also included in Table 4. Though most papers have not validated the instrument as part of its application to that study population, thirteen publications subsequent to the instrument's initial publication that do report a study population validation analysis (Ahmadi, Chung, Gibbs, & Shapiro, 2008; Chung et al., 2008; Drager et al., 2010; Friedman et al., 2010; Gami et al., 2004; Gus et al., 2008; Olivarez et al., 2010; Rasmin, 2006; Sharma, Vasudev et al., 2006; Tang et al., 2009; Weinreich, Plein, Teschler, Resler, & Teschler, 2006; West et al., 2006). In addition, among the 32 published abstracts that reported using the BQ as a research instrument ("Sleep Abstract Supplements," 2008) there was one published abstract (Steinel et al., 2007) that did not lead to publication of a full, peer reviewed paper that used a PSG-based method to validate the BQ in a bariatric surgery population.

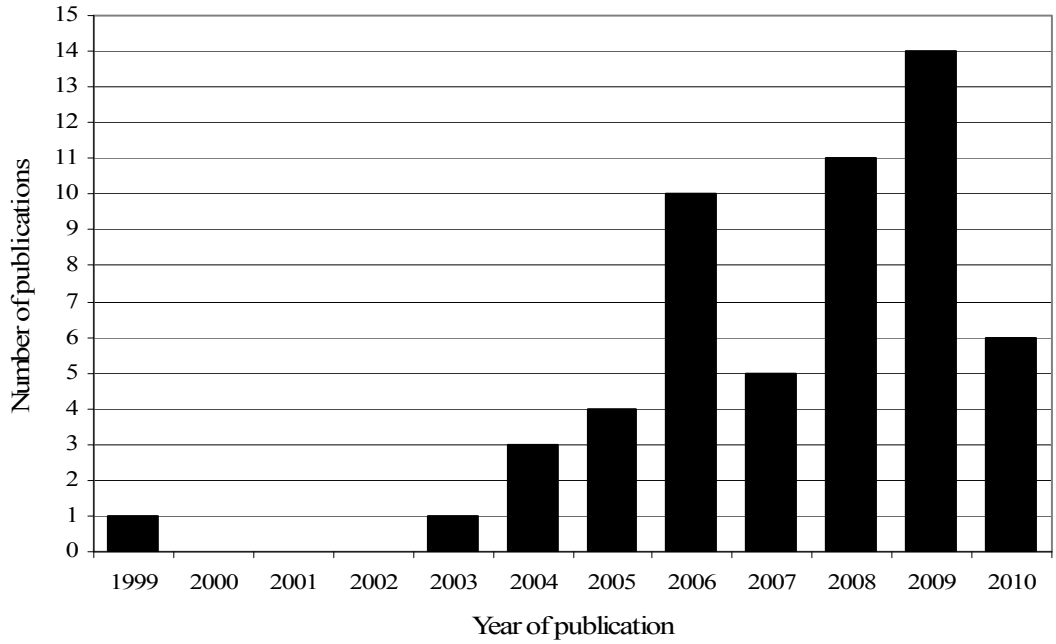

Figure 1. Research publications using the BQ

Table 4

Research Publications Using the BQ for OSA Risk Assessment Listed Chronologically

1st Author	Year	Location	Description
Netzer	1999	Cleveland	Initial validation study of BQ.
Netzer	2003	USA, Germany & Spain	Descriptive analysis of OSA symptoms & risk factors in primary care population
Calhoun	2004	Alabama	Evaluated association of OSA & aldosterone in resistant hypertension.
Gami	2004	Minnesota	Evaluated association of afib[a] with OSA, included PSG BQ validation.
Moreno	2004	Brazil	Evaluated risk of OSA among Brazilian truck drivers.
Gassino	2005	Italy	Evaluated association of oral anatomy with OSA and depression.
Mustafa	2005	Cleveland	Assessed prevalence of OSA and other sleep disorders by survey.
Principe-Rodriguez	2005	Cleveland	Assessed prevalence of OSA & other sleep disorders by survey instruments including the BQ.
Singh	2005	Winnipeg	Prevalence & association of OSA with nonalcoholic fatty liver disease.
Chen	2006	Taiwan	Analysis of OSA prevalence among those on chronic hemodialysis.
Hiestand	2006	US	Evaluated OSA by BQ in national population by telephone survey.
Moreno	2006	Brazil	Analysis regarding OSA in truck drivers, data from Moreno et al., 2004.
Padeletti	2006	Italy	Evaluated afib[a] association with OSA in those with pacemakers for bradycardia.
Rasmin	2006	Indonesia	BQ validation with portable PSG monitoring in pilot study of 15.
Sharma	2006	India	Validation study of BQ modified for Indian culture.
Tasali	2006	Chicago	OSA association with glucose tolerance in polycystic ovarian syndrome.
Vignatelli	2006	Italy	Prevalence of sleepiness, sleep quality and OSA in frontal lobe epilepsy.
Weinreich	2006	Germany	Validation of BQ in a population undergoing pulmonary rehabilitation.
West	2006	United Kingdom	Prevalence of OSA by BQ for type 2 diabetic men, PSG validation.
Chung	2007	Canada	Prevalence of OSA in a population undergoing elective surgery.
Koch	2007	Miami	Association of OSA by BQ with ischemic stroke.
Leveque	2007	Michigan	Association of OSA with central serous chorioretinopathy.
Molnar	2007	Budapest	Compares OSA by BQ in hemodialysis and kidney transplant populations.
Steinel	2007	Cleveland	Evaluated use of BQ among bariatric surgery candidates.
Ahmadi	2008	Toronto	Validation of BQ in a sleep clinic population.
Auckley	2008	Cleveland	Comparison of OSA by BQ in asthmatic& general medicine populations.
BaHammam	2008	Saudi Arabia	Determined prevalence of high risk by BQ for primary care males.
Banabilh	2008	Malaysia	Evaluated BQ association with cephalometrics in children age 7-15.
Chung	2008	Toronto	Validation of BQ, Anesthesia questionnaires in pre-surgical population
Daccarett	2008	Salt Lake City	OSA by BQ in daytime bradyarrhthmias and a control population
Gus	2008	Brazil	Analysis of OSA in resistant hypertension, PSG based validation study.
Oliven	2008	Israel	Evaluated association of airway closing pressures with OSA by BQ.
Palma	2008	Alabama	BQ used to exclude OSA in study of hepatopulmonary syndrome.
Soleo	2008	Italy	Assessed OSA prevalence by BQ & risk factor for cement workers.
Ybarra	2008	Spain	Association of OSA with ventricular dysfunction in obese females.
Adewole	2009	Nigeria	Assessed OSA prevalence by BQ among two hospitals' employees.
Alexandrov	2009	Alabama	Assessed association of OSA with blood flow steal in acute stroke.
BaHammam	2009	Saudi Arabia	Determined prevalence of high risk by BQ for primary care females.
Blondet	2009	Puerto Rico	Assessed OSA prevalence by BQ with risk factor analysis.
Brown	2009	USA, Puerto Rico	Assessed OSA prevalence & recognition in professional musicians.
Chilukuri	2009	Baltimore	BQ-based OSA used as predictor for failure after afib[a] ablation.
Facco	2009	Chicago	BQ & other sleep questionnaires used longitudinally during pregnancy.

(table continues)

1st Author	Year	Location	Description
Kapsimalis	2009	USA	Modified BQ used to assess prevalence of OSA in national sleep poll.
Khassawneh	2009	Jordan	Assess OSA prevalence by BQ among primary care patients.
Khiani	2009	USA	Assessed risk of hypoxia with endoscopy for BQ-defined OSA patients.
Lemos	2009	Brazil	BQ used for ascertainment of OSA in truck drivers.
Taj	2009	Pakistan	Assessed BQ defined OSA prevalence for public health professionals.
Tang	2009	Beijing, China	Association of OSA by BQ with afib[a] recurrence after catheter ablation.
Ybarra	2009	Spain	Evaluated correlations with BQ defined OSA in obese females.
Drager	2010	Brazil	Analysis of BQ, Epworth & metabolic syndrome in hypertensive patients.
Enciso	2010	California	Using BQ & airway dimensions to predict OSA in case-control study.
Fraser	2010	Chicago, Atlanta	OSA risk assessment in men with idiopathic intracranial hypertension.
Friedman	2010	Chicago	BQ & other OSA screening instruments combined & validated in sleep clinic population.
Olivarez	2010	Houston	Validation of BQ by PSG in 100 hospitalized pregnant females.
Sabry	2010	Egypt	Assessed sleep disorders in hemodialysis & chronic kidney disease.

[a] afib: atrial fibrillation

Among these thirteen publications and the one abstract that included a validation analysis there has been a range of reported sensitivities from 35 – 100% and specificities ranging from 20 – 95%. Table 5 collates these studies and the associated sensitivities, specificities, positive and negative predictive values from the validation analyses. Together these studies have used a variety of diagnostic criteria to define OSA. Five studies (Ahmadi et al., 2008; Chung et al., 2008; Netzer et al., 1999; Steinel et al., 2007; Weinreich et al., 2006) have done the validation analysis using multiple severity criteria with indexes (AHI or RDI) ranging from greater than five to greater than 30. The size of these studies varies ranging from 15 participants (Rasmin, 2006) to more than 200 (Friedman et al., 2010; West et al., 2006).

Data published in these studies and one abstract allow the pooling of the results from the studies that used a similar index (AHI or RDI) and criteria to define OSA. This pooled analysis of sensitivity, specificity, PPV, and NPV is an estimates of these test performance characteristics based on a larger number of patients than any of the individual studies. For example, for an index >5 a total of 1038 participants are included in the pooled analysis. Table 6 details this pooled analysis along with the 95% confidence intervals for the resulting sensitivities, specificities, PPVs, and NPVs, and the median value for these measures from the studies that contributed to each pooled analysis. This analysis demonstrates that the BQ varies in its ability to predict different levels of OSA severity across the spectrum of sleep disordered breathing.

Table 5

Studies and Abstracts Reporting BQ Validation Analyses with Sensitivity, Specificity, PPV, NPV, and Study Size

First Author	Year Published	Population Studied	OSA Criteria	Sensitivity	Specificity	PPV	NPV	*n*
Netzer	1999	Primary care patients	RDI>5	0.89	0.71	0.86	0.77	100
			RDI>15	0.97	0.48	0.54	0.97	
			RDI>30	0.92	0.35	0.17	0.97	
Gami	2004	Cardiology patients	AHI>5 & symptoms	0.86	0.89	0.97	0.60	44
Rasmin	2006	Pulmonary patients with suspected OSA	AHI>5 & symptoms	0.78	0.33	0.78	0.33	15
Sharma	2006	Medical patients with an OSA symptom	AHI>5	0.86	0.95	0.96	0.82	104
Weinreich	2006	Pulmonary rehabilitation	RDI>10	0.63	0.54	0.38	0.74	153
			RDI>15	0.67	0.53	0.25	0.85	
West	2006	Male type 2 diabetes mellitus	ODI>10 & + PSG[a]	0.75	0.54	0.27	0.91	238
Steinel	2007	Bariatric surgery candidates	AHI>5	0.83	0.20	0.93	0.08	75
			AHI>15	0.86	0.22	0.70	0.42	
Ahmadi	2008	Patients referred to psychiatry based sleep clinic	RDI>5	0.68	0.49	0.50	0.67	130
			RDI>10	0.62	0.43	0.28	0.76	
			RDI>15	0.57	0.41	0.21	0.78	
Chung	2008	Preoperative patients for elective surgery	AHI>5	0.69	0.56	0.78	0.45	177
			AHI>15	0.79	0.51	0.51	0.78	
			AHI>30	0.87	0.46	0.32	0.93	
Gus	2008	Patients with resistant and controlled hypertension	AHI>10	0.86	0.65	0.75	0.79	126
Tang	2009	Recurrence of atrial fibrillation after catheter ablation	AHI>5	1.00	0.30	0.74	1.00	30
Friedman	2010	Sleep clinic patients	AHI>5	0.62	0.23	0.67	0.18	223
Drager	2010	Hypertensive adults	AHI>5	0.93	0.80	0.75	0.56	99
Oliverez	2010	Hospitalized pregnant women	AHI>5	0.35	0.64	0.19	0.64	100

[a] This study validated the BQ with a two-stage process requiring an ODI>10 by overnight oximetry before undergoing full PSG. The criteria for OSA on PSG were not published.

Table 6

BQ Summary Performance Measures for Validation Studies Pooled by Severity Criteria

		Sensitivity	Specificity	PPV	NPV	Total *n*	Studies included
AHI or RDI>5 without regard to symptoms	Pooled value	0.74	0.57	0.72	0.59	1038	Ahmadi, Chung, Drager, Friedman, Netzer, Oliverez, Sharma, Steinel, Tang
	(95% CI)	(0.71-0.77)	(0.54-0.60)	(0.69-0.75)	(0.56-0.62)		
	Median	0.83	0.56	0.75	0.64		
AHI or RDI>5 with daytime symptoms	Pooled value	0.84	0.75	0.93	0.55	56	Gami, Rasmin
	(95% CI)	(0.75-0.94)	(0.63-0.86	(0.86-1.00)	(0.42-0.68)		
	Median	0.79	0.51	0.78	0.60		
AHI or RDI>10 without regard to symptoms	Pooled value	0.75	0.54	0.51	0.77	566	Ahmadi, Chung, Gus, Weinreich
	(95% CI)	(0.71-0.78)	(0.50-0.58)	(0.47-0.55)	(0.73-0.80)		
	Median	0.75	0.50	0.35	0.78		
AHI or RDI>15 without regard to symptoms	Pooled value	0.73	0.42	0.36	0.78	357	Ahmadi, Netzer, Steinel, Weinreich
	(95% CI)	(0.69-0.78)	(0.37-0.48)	(0.31-0.41)	(0.74-0.82)		
	Median	0.79	0.48	0.51	0.78		
AHI or RDI>30 without regard to symptoms	Pooled value	0.88	0.42	0.26	0.94	277	Netzer, Chung
	(95% CI)	(0.85-0.92)	(0.48-0.36)	(0.21-0.31)	(0.91-0.97)		
	Median	0.90	0.41	0.25	0.95		

To assess which level of severity is best predicted by the BQ several characteristics can be considered, (a) likelihood ratios (LR), both positive and negative (R Jaeschke, G. Guyatt, & J. Lijmer, 2002); (b) the Youden *J* statistic (Youden, 1950); and (c) the diagnostic odds ratio (Deeks, 2001). The diagnostic odds ratio (DOR) is a single summary measure of diagnostic performance that combines measures of sensitivity, specificity, positive and negative likelihood ratios (Deeks, 2001). Higher diagnostic odds ratios, positive likelihood ratios, lower negative likelihood ratios and a larger Youden's *J* statistic are indicative of stronger diagnostic performance (Deeks, 2001; R. Jaeschke, G. Guyatt, & J. Lijmer, 2002; Youden, 1950). Thus, as depicted in Table 7 below, the BQ best predicts OSA with an AHI > 5 with daytime symptoms. However, given the relatively small number of participants (n = 56) contributing to this measure, and the resulting wide confidence interval, the questionnaire also performs favorably in predicting OSA with an AHI>5 without regard to symptoms. This later level of severity without a daytime sleepiness requirement again was the one considered in the OSA population prevalence analysis of Table 1 above.

Table 7

BQ Diagnostic Performance at Different Levels of OSA Severity

OSA Severity	LR +	LR -	DOR	Youden's *J* (95% CI)
AHI or RDI>5 without regard to symptoms	1.72	0.46	3.75	0.31 (0.25 – 0.37)
AHI or RDI>5 with daytime symptoms	3.31	0.21	15.73	0.59 (0.46 – 0.73)
AHI or RDI>10 without regard to symptoms	1.62	0.47	3.46	0.29 (0.25 – 0.33)
AHI or RDI>15 without regard to symptoms	1.41	0.47	2.99	0.23 (0.19 – 0.27)
AHI or RDI>30 without regard to symptoms	1.52	0.28	5.53	0.30 (0.26 – 0.43)

In summary, the BQ, first published in 1999, is an instrument designed to identify OSA risk based on tabulation and scoring of symptoms related to snoring and daytime sleepiness along with the presence of hypertension and obesity. The instrument has been used in 53 original studies including fourteen that included validation of the instrument against a PSG based gold standard. There has been subtle variability in the questions and scoring algorithm for the instrument, though the structure of the instrument has been generally consistent. The instrument's diagnostic performance has also been variable. As one might expect for an instrument based on OSA symptoms, it performs best in predicting OSA with day-time symptoms, and not as well for OSA without a daytime sleepiness criteria. For the range of severity without daytime symptoms, the BQ performs best for mild OSA with an AHI (or RDI) greater than five.

A Population-based Laboratory: The Rochester Epidemiology Project

Kessler and Levin (1970) suggest that the epidemiologic study of a community as a population-based laboratory began with the very founding of epidemiology as a science in the sanitary surveys of the 19th century by Chadwick and Shattuck, respectively. They (Kessler & Levin, 1970) argue that the most persuasive reasons for choosing a community for epidemiologic study are "pragmatic and administrative" (p. 8). The Rochester Epidemiology Project (REP) is one such population-based laboratory that has developed because of several local circumstances, some going back to the late 19th and early 20th centuries. In this study, the REP provided a unique opportunity to use clinical record systems in a population-based study.

When Dr. William W. Mayo, established his practice in Rochester in the 1860s Rochester was a frontier center of commerce in southern Minnesota but was rather isolated from the growing Minneapolis and St. Paul area about 90 miles away and other developing health care centers (Clapesattle, 1990). As that practice grew from a partnership of a few physicians to a multi-specialty group practice a single medical record for each patient that would be shared by all of the group's physicians was developed by Dr. Henry Plummer in 1907 (Kurland & Molgaard, 1981). In order to facilitate research and teaching Plummer and his secretary, Mabel Root, developed record index systems based on (a) diagnoses by organ system, and (b) surgical procedures which were known as the Plummer-Root indexes. As diagnostic techniques and pathogenic understanding improved, in the 1930s Dr. Joseph Berkson developed a revised diagnostic coding system combined with an early Hollerith punch card automated indexing and sorting technology that became known as the Berkson file (Berkson, 1936). This coding system was used until 1974 when a modified Hospital Adaptation of the International Classification of Diseases, second edition (H-ICDA-2) coding system, originally published by the World Health Organization, was adopted (Kurland & Molgaard, 1981). As a unified multispecialty medical practice with a single record for each patient documenting all care provided, the systematic indexing of these records by diagnosis and surgical procedures created a substantial opportunity for clinical and epidemiologic research.

The relative isolation of Rochester from other larger medical centers, and with the presence of virtually every specialty and subspecialty within the Mayo Clinic, the people

of Olmstead County where Rochester is located have little need to seek care from a spectrum of providers across a broad, potentially multi-state region; rather they are able to obtain nearly all of their care locally (Melton, 1996). There are several providers of care in Olmstead County outside of Mayo Clinic, most notably the Olmstead Medical Center which developed in the 1950s ("Learn about OMC: Our history," 2008) and now includes over 150 providers (Yawn, 2008). In addition there are a handful of other private practitioners, several nursing homes, governmentally provided public health services, and Veteran's Administration system in the region. Thus, in 1966 what would become the Mayo Department of Health Science Research, in partnership with these other Olmstead County and regional healthcare providers, received National Institutes of Health funding to support the collection, archiving, and medical record linkage for records from all of these health care institutions, and the vital records for the county (Erickson, Pankratz, Schrage, & Stotz, 2007; Melton, 1996). Through 2004 this record linkage system has supported the publication of more than 1500 clinical and epidemiologic research papers (Rocca & Yawn, 2008). With this comprehensive record linkage system and a nearly century long record system archive, the REP is a unique laboratory in which to do longitudinal population-based epidemiology research (Melton, 1996).

The REP uses a probabilistic method to assign records from multiple sources to a single master REP identification number along with all records later received for that participant. This probabilistic method utilizes the following demographic information: last name, first name, middle name, suffix, gender, birth date, social security number, and geographic residency. Hand matching of individual records is used when missing

demographic information makes probabilistic matching impossible. As of 2008 about 1.53 million records from 50 different sources have been matched to 788,130 unique patients (J. St. Sauver, personal communication, October 8, 2008).

To assess the reliability of the system a random sample stratified by age of 400 REP participants was manually examined to identify records incorrectly linked to these individuals and to identify any additional records that should have been linked to these participants. The REP system had matched a total of 1333 records to these 400 participants with 2.5% (95% Confidence interval: 1.2 – 4.6%) of these individuals having incorrectly matched records. In addition, 1.3% (95% Confidence interval: 0.4 – 2.9%) of these participants appeared to have additional records that should have been matched (J. St. Sauver, personal communication, October 8, 2008).

> Together, these data suggest that the REP computer matching algorithms perform extremely well in correctly identifying and linking medical records from multiple institutions to single individuals, even when individual medical records have multiple names, multiple spellings of names, name changes, and spelling errors (J. St. Sauver, personal communication, October 8, 2008).

The REP has been identified by at least two groups as one of only six population-based medical record linkage systems in the world that are comprehensive in both the spectrum of diagnoses and the settings in which care is provided (Brameld, Holman, Lawrence, & Hobbs, 2003; Holman, Bass, Rouse, & Hobbs, 1999). The other similar systems include the Oxford Record Linkage Study (Goldacre, Kurina, Yeates, Seagroatt, & Gill, 2000), the Scottish Record Linkage System (Kendrick & Clarke, 1993; Walsh,

Smalls, & Boyd, 2001), the Population Health Information System in Manitoba (Roos et al., 1995), the British Columbia health database (Chamberlayne et al., 1998), and the Western Australian Health Services Research Linked Database (Holman et al., 1999). Thus, the REP may be the only comprehensive record linkage system in the United States.

In the course of developing the Western Australia database Holman and colleagues (1999) studied and visited all of the identified databases except that found in British Columbia. In the course of this evaluation they developed a "set of benchmarks for international best practice" (p. 457) for such databases (Holman et al., 1999). A list of the benchmarks and a description of the REP relative to each benchmark is provided in Table 8.

Subsequently a similar set of general guidelines for comprehensive linkage systems has developed recognizing that such systems each develop in very different contexts (D.A. Holman, personal communication, October 5, 2008). Those guidelines are as follows:

> Population: The population covered by the system is ideally geographically defined and relatively stable, of adequate size for most analyses (ideally >1 million) and with adequate longitudinal coverage (>10yr). The advantage of a geographically defined population, as distinct from register-based populations such as members of a health insurance plan, is that research based on the former will enjoy the greater external validity gained from a study population more representative of the general community.

Data resources: Health events and other data should be ascertainable for the whole population (not merely a sample or population subgroup) on a continuous basis (not an ad hoc or intermittent basis). The range of data resources should be sufficient to address the research agendas of primary interest. Linked hospital morbidity data and deaths are arguably the minimal system, but ideally the system should include ambulatory health service encounters, key disease registers, birth and perinatal data and a population register such as an electoral roll.

Technical facilities: Linkage should be achieved by either high performance probabilistic matching or a reliable unique person identification number or a hybrid of these methods. A program of data validation and assessment of linkage performance is highly desirable. A tracing system is desirable to censor patients who emigrate from the geographic area and are therefore lost to longitudinal follow-up. Geocoding of addresses will enhance the capacity for spatial analysis and assignment of socio-economic status and remoteness indices.

Organisational [*sic*] supports: These include a governance structure for leadership and management of the data linkage enterprise; instruments for co-operation between agencies providing data (eg, MOUs); consumer participation; a facilitative or at least nonobstructive legal framework; and multidisciplinary research teams including collaboration with health service providers (D.A. Holman, personal communication, October 5, 2008).

Table 8

International Benchmarks for Record Linkage and Health Services Research Databases

Benchmark (Holman et al., 1999, p. 458)	REP description relative to benchmarks
1. Population 1.1 Geographically defined and relatively stable 1.2 Adequate size for most analyses (ideally >1 million) 1.3 Adequate longitudinal population coverage (>10 yr)	The REP is geographically defined as the residents of Olmsted County, Minnesota. For Olmstead County in the six years from 2000-2006 there was a net in-migration of 3.35% of the 2000 population, the second highest rate by county in the state (US Census Bureau, 2008c). The population is estimated to be 137,521 in 2006, smaller than referenced in this benchmark (US Census Bureau, 2008b). However, during the course of its existence the REP has matched more than 750,000 unique individuals (J. St. Sauver, personal communication, October 8, 2008). REP allows record review for 50 or more years (Melton, 1996)
2. Data Resources 2.1 Named population register 2.2 Socio-demographic data from the Census 2.3 Birth and death registrations 2.4 Perinatal events 2.5 Hospital in-patient data 2.6 Physician contacts 2.7 Pharmaceutical benefits data 2.8 Laboratory services data 2.9 Cancer notifications 2.10 Domiciliary care data 2.11 Residential care data 2.12 Residential care data 2.13 Health survey data	The REP has grown to include data from essentially all medical care providers within the county and many providers elsewhere in the region that might have occasion to provide care to Olmsted County residents. It includes hospital, nursing home, state mental hospital, veterans administration, and prison health facilities. Public health records including birth and death registrations are part of the database. The REP, however, does not have direct participant linkage to socio-demographic census data, and does not include pharmaceutical benefit data. To the extend laboratory services were provided through a medical care provider indexed in REP this laboratory data is included. Currently home health care agency data is not included. The REP is not linked to NHANES (US Centers for Disease Control and Prevention, 2008b) participants that might live in Olmsted County, and the county is not currently in the BRFSS (US Centers for Disease Control and Prevention, 2008a).
3. Technical systems 3.1 Unique person identification number 3.2 High performance probabilistic matching 3.3 A program of validation studies 3.4 Facility for follow-up (tracer systems) 3.5 Facility for geocoding and spatial analysis	The REP does use a REP master identification number to match records once received from various sources. The social security number is one demographic identifier used in the probabilistic matching. Validation of REP probabilistic matching is done as reported above (J. St. Sauver, personal communication, October 8, 2008). There is no formal follow up tracer system to eliminate those that have emigrated. However, study designs can be used to censor participants at the latest recorded care provided. Participants' residential addresses are geocoded to facilitate spatial analysis (Erickson et al., 2007).
4. Organizational Supports 4.1 Multidisciplinary research team 4.2 Supportive legal framework 4.3 Federal health agency cooperation 4.4 State health agency cooperation 4.5 Health care practitioner collaboration	The REP involves a long term multi-disciplinary research team including epidemiologists, information technologists, programmers, physicians, nurses, and other clinicians (Erickson et al., 2007). Veterans Administration facilities and state health department are federal and state agencies that historically had cooperated with the REP, though currently new relationships to provide current records to the REP are being negotiated (J.J. Pankratz, personal communication, October 14, 2008). State mental health institutions have also been partners in the project (Erickson et al., 2007). The REP has been able to engage essentially all health care practitioners in the county, as well as many in neighboring counties (Melton, 1996).

Thus, it appears that the REP is a record linkage system that has validated linkage performance, is internationally recognized and substantially meets available benchmarks and guidelines for such systems. The REP provided a unique opportunity to use clinical record systems for population-based study, such as the analysis of the prevalence of clinically recognized obstructive sleep apnea in this study.

A Population-based Sample: The Prevalence of Asymptomatic Ventricular Dysfunction

In 1997 a population-based sample was drawn in Olmstead County, Minnesota for the purpose of longitudinally studying asymptomatic cardiac ventricular dysfunction. That study, known as the prevalence of asymptomatic ventricular dysfunction (PAVD) study, included an assessment of OSA risk as part of the longitudinal follow up of participants for the study's second round. With the availability of this population-based assessment of OSA risk in this study, the participants in the study provided the sample in which the prevalence of clinically recognized OSA was assessed. Thus, the literature regarding the establishment and nature of this study sample are reviewed.

The initial sample for the PAVD study was drawn, using the resources of the Rochester Epidemiology Project (REP) (Melton, 1996), from the residents of Olmsted County, Minnesota who were 45 years of age or older on January 1, 1997 (Redfield et al., 2003). At that time the total population of the county by linear interpolation from the decennial censuses of 1990 and 2000 was 118,931 (US Census Bureau, 2008a). A 7% random sample of each 5 year age and gender strata were selected for participation (Ammar et al., 2006) including a total of 4203 potential participants (Redfield et al.,

2003). Of those invited, a total of 2,042 (47%) participated in round one of the study (Redfield et al., 2003).

In round one of the study participants completed a 17-page questionnaire regarding health behaviors, evidence of cardiovascular disease, and functional status. In addition, participants completed a physical examination, pulmonary function testing, electrocardiogram, and an echocardiogram (Jacobsen et al., 2004). Using the REP, participants' medical records were reviewed by trained nurse abstractors for evidence of hypertension, myocardial infarction, coronary artery disease, diabetes mellitus, and congestive heart failure based on specific criteria (Redfield et al., 2003). This record abstraction did not record clinical data related to sleep-disordered breathing.

A study (Jacobsen et al., 2004) was done of the first 963 persons receiving invitations to participate in the study that included 488 (51%) who completed all aspects of PAVD round one. Participation rates by gender were not appreciably different with 52.7% of men, and 49.0% of women, participating. Participation by the youngest (age 45-54 years) and oldest (age ≥75 years) groups, ranging from 34.9 to 45.4%, were lower than the remainder (age 55-74 years) which ranged from 58.0 to 61.3%. Using the resources of the REP analysis of potential associations between disease diagnoses and participation was carried out. Participation was not different among those with and without a prior history of coronary artery disease, congestive heart failure, other cardiovascular diseases, diabetes or other co-morbidities. However, those with chronic obstructive pulmonary disease (COPD), even after adjusting for age differences, were less likely to participate than those without COPD (19% vs 51%). This study (Jacobsen et

al., 2004) concluded that there was "some reassurance that participation bias in this study may have little influence on its overall findings, although this cannot be conclusive" (p. 579).

For round two of the study, beginning in 2001 all participants that had completed round one were invited to participate approximately four years after their initial round one assessment (Rodeheffer et al., 2000). A total of 1,402 participants participated in Round Two of the study involving a follow up questionnaire, physical examination, electrocardiogram, blood sample, and echocardiogram. The round two PAVD questionnaire included the BQ items as described for PAVD in Table 3 above.

Trained nurse abstractors again reviewed round two participants' medical records using the resources of the REP to obtain the following information: sociodemographic information; cardiovascular diagnostic evaluations, diagnoses, and treatment; and laboratory samples for potential testing of lipid profiles, thyroid studies, and hematocrit were obtained (Rodeheffer et al., 2000). In this record review and abstraction clinical data related to sleep-disordered breathing again was not part of the protocol.

With the PAVD study, round two now including a uniform assessment of OSA risk using the BQ, the study provided an assessment of the prevalence of the clinical recognition of OSA in a population-based sample.

Summary

This literature review has considered a variety of aspects of the epidemiology, diagnosis, and treatment of OSA, previous reports of the prevalence of the clinical recognition of OSA, the performance of the BQ, and nature of the Rochester

Epidemiology Project as community-based laboratory. This final section attempts to summarize this data as it relates to the planned study of the prevalence of clinically recognized OSA in a population based sample.

OSA is a disorder in the continuum of sleep-related breathing disorders. A quarter century of prevalence studies suggest that it is relatively common with 19 – 25% of adult men having OSA defined as an AHI $\geq$ 5 without regard to daytime sleepiness. The disorder has a somewhat lower prevalence in women with a gender ratio of about 2:1, and increases in prevalence with age up to about 65 years. Obesity, snoring, daytime sleepiness, hypertension, and male gender are all considered risk factors for OSA. Full laboratory PSG is the gold standard diagnostic technique for OSA, though the less cumbersome techniques of in home monitoring are gaining favor. CPAP is the first-line therapy for OSA whereas dental appliances and surgical treatment can play a role in selected patients. OSA is associated with increased risk of hypertension, cardiovascular, and cerebrovascular disease. Unfortunately CPAP is a therapy that is difficult to adhere to limiting the risk reduction associated with treatment for these associated diseases.

Studies prior to 1990 suggested that the prevalence of clinically recognized OSA among those with OSA was no more than 1%. Two subsequent population-based studies using data from the 1990s showed that clinical recognition of OSA could be as high as 7% and 18% in women and men, respectively. Among the limitations of these studies was the use of a self-reported OSA diagnosis. Among the explanations for the limited clinical recognition has been (a) limited OSA awareness by physicians, (b) limited access to diagnostic sleep laboratories and sleep specialists, and (c) the intrusive nature and

expense of PSG. There is evidence that there has been improvement in all of these factors over that past decade.

The BQ is a simple survey instrument developed in the late 1990s to assess individuals' risk of OSA. In recent years there has been a growing research use of the instrument with a total of 53 publications now reporting its use. In a pooled analysis of the fourteen studies that have validated the instrument against a PSG standard, the instrument's performance varies with the level of OSA severity inclusion criteria used. It performs best in detecting OSA defined by an AHI ≥ 5 both with and without a daytime symptom criteria.

This study used REP resources to assess the prevalence of clinically recognized OSA among those with OSA based on the BQ. The REP is a longitudinal clinical record linkage system for the population of Olmsted County, Minnesota. Historically this system developed as a result of the unified, shared medical record developed at the Mayo Clinic in 1907 that has since evolved and been linked with the records of essentially all health care providers in the region along with birth and death records through the support of the National Institutes of Health beginning in 1966. The REP is identified as one of only six comprehensive record linkage systems internationally, and the only such system in the United States.

The PAVD study is a population-based longitudinal study primarily considering myocardial ventricular function in which participants had a rather comprehensive evaluation and medical record abstraction focused on cardiac risk factors, initially and approximately four years later. Though no assessment or record review of sleep-related

breathing problems was included in either the first or second round of the study, the survey instrument for round two included a modified BQ that identified those at high risk for OSA in a consistent manner.

Thus, the literature suggests that OSA is rather prevalent disorder that historically has been substantially under recognized clinically. The BQ is a reasonable instrument by which to classify participants' risk of OSA as has been done in Round two of the PAVD study. With use of REP resources, participants in the PAVD study with clinically diagnosed OSA were identified, and the prevalence of OSA clinical recognition among those at high risk for OSA was assessed.

CHAPTER 3: RESEARCH METHOD

Introduction

OSA is a sleep-related breathing disorder that is associated with significant cardiovascular and cerebral vascular morbidity and mortality. Treatment with CPAP, considered to be the first-line OSA treatment, does attenuate this increased morbidity and mortality. However, patient adherence to CPAP therapy is challenging and is limited. More importantly most OSA is undiagnosed and thus untreated. Previous research has shown that no more than 18% of prevalent OSA was clinically diagnosed in the 1990s. Lack of physician awareness of OSA, access to sleep lab services and sleep medicine specialty treatment had provided explanation for this under recognition. There is evidence that there is now improved physician awareness and access to sleep medicine services. Thus, this study assessed the prevalence of clinically recognized OSA among those at high risk for OSA in a community-based sample.

The methods used to identify those considered to be at high risk for OSA, and the method for identifying those participants in the sample that have been clinically recognized with OSA are described in this chapter. The methods used for data collection and analysis, and measures taken to protect participants' rights are also described.

Research Design and Approach

This study utilized the community based sample established in 1997 for the ongoing study titled the Prevalence of Asymptomatic Ventricular Dysfunction (PAVD) Study (Redfield et al., 2003) to evaluate the prevalence of clinically recognized OSA among those with BQ defined OSA. As described in chapter 2 round two of the PAVD

study included a modified BQ. Thus, participants in this sample were classified as either high or low risk for OSA. This study then used the resources of the Rochester Epidemiology Project including the patient database, clinical record access system, and technical support staff, to identify all PAVD participants that had the clinical diagnosis of OSA. The analysis of this data identified factors predictive of clinical recognition, and assessed whether there was evidence of increased OSA clinical recognition among those at high risk for OSA compared to the previous studies of OSA clinical recognition.

In the two previous assessments (Kapur et al., 2002; Young, Evans et al., 1997) of the prevalence of clinically recognized OSA, the participant's self-reported physician diagnosis was used as the marker of OSA clinical recognition. Although one of these studies used a laboratory-based PSG to determine the presence of OSA in the population (Young, Evans et al., 1997), the other study (Kapur et al., 2002) used as an OSA proxy of self-reported symptoms of frequent snoring and excessive daytime sleepiness. Though these factors are recognized as OSA risk factors, this two-symptom proxy had never been validated as an OSA predictor, even in the sources cited by Kapur and colleagues (2002) in support of its use (Bradley et al., 1998; Newman et al., 2001; Strohl & Redline, 1996). Thus, the use of medical record verification of the clinical diagnosis of OSA, along with a previously validated instrument, the BQ, as the OSA proxy, represented an improved method over previous studies in this area. In addition, performing this study based on data collected from 2001 to 2010 will represent a timely reevaluation following improved physician recognition and sleep medicine access in the 1990s (Namen et al., 2002).

Setting and Sample

This study was carried out using the population-based community sample established for the PAVD study as previously described in chapter 2 (Ammar et al., 2006; Redfield et al., 2003). That sample was drawn from the residents of Olmsted County Minnesota who have access to sleep medicine services through the Mayo Clinic Center for Sleep Medicine, one of the largest such centers in the United States ("Mayo Clinic: Obstructive Sleep Apnea, Diagnosis," 2008), and the Olmsted Medical Center sleep program ("Olmsted Medical Center: Services, Sleep Medicine/Lab," 2008). Thus, these participants have substantial local access to sleep diagnostic and treatment services.

The sample used for this study was the participants that continued in round two of the PAVD study. As described in chapter 2, this round two sample represents those participants that had completed round one of the study who then chose to continue their participation in round two. This study then analyzed this sample for participation bias comparing these round two participants with those from round one who did not participate in round two. A previous analysis for participation bias comparing those participating in round one, with those invited to participate in round one but choosing not to do so, had been carried out (Jacobsen et al., 2004). The relationship of this analysis with the previous participation bias analysis (Jacobsen et al., 2004) after which it was modeled is graphically demonstrated in figure 2. Note that because previous PAVD analyses had been focused on echocardiographically defined endpoints, previously reported participation totals had been based on completion of the echocardiogram

(Redfield et al., 2003). This study focused on completion of the BQ, therefore the numbers of participants deviate slightly from those previous reports.

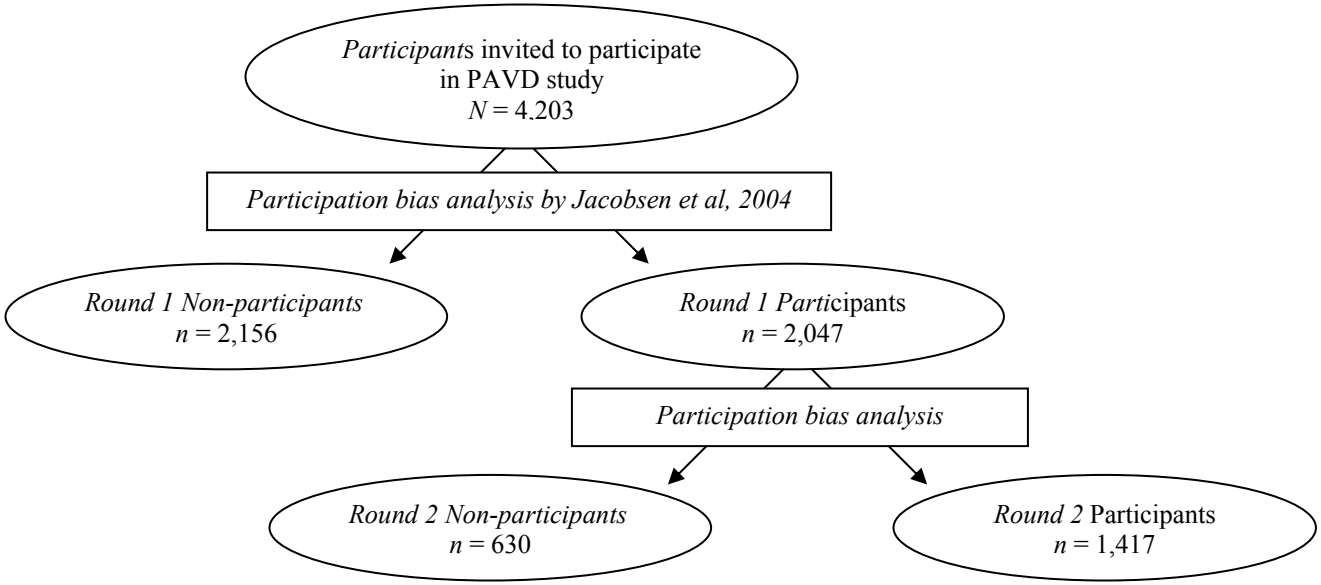

Figure 2. PAVD participation bias analyses

Power and Sample Size

This study planned to detect a change in the prevalence of OSA clinical diagnosis among those at high risk for OSA compared to previous studies (Kapur et al., 2002; Young, Evans et al., 1997). These earlier studies had demonstrated prevalence of clinical recognition among those with OSA as shown in Table 9.

Table 9

Prevalence of Clinical OSA recognition among those with OSA

Study	Gender	Prevalence of Clinical OSA Recognition among those with OSA	Number with OSA (*n*)
Young, Evans et al., 1997	Male	0.18	77
Young, Evans et al., 1997	Female	0.07	27
Young, Evans et al., 1997	Combined	0.154	104
Kapur et al., 2002	Combined	0.082	650

With this study being part of a larger longitudinal study, the sample size has been fixed by the design and participation rates in rounds one and two of the overall PAVD study. Thus this analysis of power and sample size considered the power of this study using this sample to detect a difference in the prevalence of OSA clinical recognition from these previous studies.

The design considered the proportion of those with clinically recognized OSA in round two of the PAVD study compared to the two previous studies (Kapur et al., 2002; Young, Evans et al., 1997). Thus, this represents a comparison of two binomial proportions resulting from independent samples. A method for calculating the power in such circumstances has been described (Rosner, 2006) that involves the following

parameters as applied to this study: the proportion with clinically recognized OSA in the two samples (p_1 and p_2), the difference in the proportions in the two samples (Δ), the complimentary proportion with clinically unrecognized OSA in each sample (q_1 *and* q_2), the average of the proportions and the complimentary proportions in the two samples ($\overline{p}$ and $\overline{q}$), the number of participants, in this case with OSA, in the two samples (n_1 and n_2), and the level of statistical significance (α) where phi (Φ) is the cumulative distribution function of a standard normal distribution. From Rosner (2006) that calculation takes the following form (p. 418):

$$Power = \Phi\left[\frac{\Delta}{\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}}} - z_{1-\alpha/2}\frac{\sqrt{\overline{pq}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}}{\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}}}\right]$$

A preliminary analysis of the BQ results from PAVD round two classified a total of 527 participants as being at high risk for OSA including 328 men and 199 women with these participants representing the sample size (n_2) in the study for the comparisons with previous reports. Use of the high risk classification on the BQ as an OSA proxy then provided the denominator for calculation of the prevalence. With increased physician awareness of OSA and increased availability of sleep laboratories as described in chapter 2, it was highly unlikely that the clinical recognition of OSA would have decreased compared to that noted in the 1990s. Thus, a one-sided power analysis with a z term of $z_{1-\alpha}$ is used here rather than $z_{1-\alpha/2}$ as described above by Rosner (2006).

For this study this method of power calculation (Rosner, 2006) was used to determine the largest prevalence difference that can be detected with a power of at least 80% relative to the four previously reported prevalence rates. As illustrated in Table 10 below, an increase in the prevalence of 0.171 compared to the previously reported prevalence would be detected with a power of 0.80 for females. For males and the two previously reported prevalence values for combined gender populations, there is a 0.80 power to detect even smaller increases in prevalence as demonstrated in Table 10. Thus, this study had a power of 80% to detect an increase of prevalence of clinically recognized OSA to 31% in males, 24% in females, and 26% in a combined gender population with the probability of type I error less than 5%.

Table 10

Power Analysis: Minimum Prevalence Increase Detected with a Power of ≥0.80 Based on a One-sided Analysis

Gender	Number with OSA or proxy in original study (n_1)	Number with OSA proxy in proposed study (n_2)	Original prevalence (p_1)	Prevalence increase detected with a power of 0.8 (Δ)	Prevalence detected with a power of 0.8 (p_2)
Male (Young, Evans et al., 1997)	77	328	0.180	0.133	0.313
Female (Young, Evans et al., 1997)	27	199	0.070	0.171	0.241
Combined (Young, Evans et al., 1997)	104	527	0.154	0.105	0.259
Combined (Kapur et al., 2002)	650	527	0.082	0.045	0.127

Instrumentation and Materials

Berlin Questionnaire

As part of the PAVD round two evaluation participants completed a 21-page survey developed by the PAVD investigators in cooperation with the Mayo Survey Research Center titled "Olmsted County Heart Survey." That instrument included a wide variety of questions related to cardiovascular symptoms, and previous cardiovascular care, and was largely similar to the 17-page survey previously used in round one. The items from the BQ, with the exception of items eight and nine related to nodding off while driving (see Table 3 above), were included in the round two questionnaire. As described previously, after review by legal counsel these items were omitted from this questionnaire due to concerns about vicarious liability associated with recording participants' propensity for nodding off while driving without ability to intervene in the research setting (A.S. Gami, personal communication, July 17, 2007).

The BQ is, as originally described (Netzer et al., 1999; "Reprinting of the Berlin Questionnaire," 2000), an 11 item survey instrument that considers three categories of symptoms and conditions associated with OSA. Those three categories are (a) snoring, (b) daytime fatigue and sleepiness, and (c) the presence of hypertension and obesity. For these categories there are five, four, and two items, respectively, in the instrument's original presentation each with either binary scoring, or scoring based on a five-point ordinal scale of severity (Netzer et al., 1999; "Reprinting of the Berlin Questionnaire," 2000).

As described in chapter 2 the BQ has been used as a research instrument in 53 previous publications including fourteen that published a validation study for the instrument with a PSG-based diagnostic method for OSA as the gold standard. Though the overall structure of the instrument has been consistent in these studies, there have been a number of variations in the questions scored, and the exact scoring methods used in these studies. The details of these variations are described in chapter 2.

In pooled analysis of these validation studies (see Tables 6 and 7) the BQ appears to perform best in predicting OSA defined by an AHI or RDI>5 with or without daytime symptoms. Thus, the BQ, used in this manner, is an appropriate instrument to use in predicting OSA in the proposed study population.

Using the REP for identification of PAVD participants with clinical OSA diagnosis

The REP, as described in chapter 2, is a comprehensive medical record data linkage system that allows population-based study of a wide variety of health phenomena in Olmsted County, Minnesota (Melton, 1996). Using a method typical for studies using the REP, the PAVD study had originally been initiated using REP resources to randomly select a population-based sample of those ages 45 and older on January 1, 1997 from the overall county population (Ammar et al., 2006; Redfield et al., 2003). With the REP's comprehensive data linkage system, it was possible to use REP resources to electronically return to the PAVD sample and identify participants likely to have undergone PSG or carry a clinical diagnosis of OSA.

This was accomplished through the identification of the medical procedure billing and diagnostic codes potentially associated with PSG, OSA and other sleep-related

breathing disorders, and with the first-line therapy for OSA, CPAP. Then the medical records identified through the REP were reviewed to identify details of the diagnostic evaluation, the actual clinical sleep diagnosis, and the nature of any associated treatment. This study identified all participants from round one (which includes all round two participants) that had undergone PSG or carried a diagnosis of OSA. The inclusion of the round one participants that did not participate in round two allowed a comparative analysis of those participants with round two participants for possible participation bias.

In Olmsted County there are two sources of sleep laboratory evaluation, one at the Mayo Clinic, and the second at Olmsted Medical Center. A comprehensive electronic database of the PSGs performed at Mayo Clinic is available. Thus, as iterations of the REP search criteria for PSG, OSA, and sleep-related diagnoses were developed, the resulting patient population was compared to the Mayo Sleep Laboratory Database (MSLD) as a means of assessing the performance of the search criteria in identifying all PAVD participants known to have had PSG performed in the Mayo Clinic Sleep Laboratory. This comparison of the participants identified using the REP search with roster of those already known to have undergone a Mayo PSG provided an indirect method of evaluating the validity and efficiency of the REP search criteria as they were developed.

In the developing a search strategy for this study the first iteration of REP criteria was as follows: Either a PSG or CPAP procedure code AND one of a broad, inclusive list of sleep breathing-related diagnostic codes. The list of the codes selected is displayed in Table 11. This iteration of the search identified 169 participants from the 2,042

participants that completed round one of the PAVD study. These 169 participants included 151 of the 235 PAVD participants known to have had a PSG based on the MSLD, and 18 additional participants. These 18 participants included 16 that were found to have had a PSG at the Olmsted Medical Center, one found to have had a PSG at Mayo Clinic that was not recorded in the MSLD, and an additional participant whose clinical records note an OSA diagnosis, but make no reference to when or where a PSG might have been performed. With 152 of these 169 participants having had PSGs performed at Mayo Clinic, whereas 16 were performed at Olmsted Medical Center, an approximate 9.5:1 ratio of studies performed in the two institutions was demonstrated.

Table 11

Sleep Breathing-related Diagnostic Codes

Code	Description
7735110	Insomnia, NOS
7735111	Disorder, Sleep, NOS
7735112[a]	Deprivation, Sleep
7735113	Disturbance, Sleep
7735115	Insufficiency, Sleep (Syndrome)
7735120	Sleepiness, NOS
7735130	Sleepiness, Cause Specified
7735132	Disorder, Excessive Somnolence
7781510	Hypoventilation, NOS
7781511	Syndrome, Hypoventilation, NOS
7781520	Syndrome, Hypoventilation, Cause Specified
7781521	Hypoventilation, Cause Specified
7782210	Respiration, Cheyne-Stokes, NOS
7782211	Cheyne-Stokes See Also Respiration
7782220	Respiration, Cheyne-Stokes, Cause Specified
7782410	Apnea, NOS
7782411	Apnea, Sleep
7782412	Sleep, Disordered Breathing
34199754	Clinic, Sleep Disorder Center
327.1	Organic Hypersomnia, Unspecified
327.11	Idiopathic Hypersomnia With Long Sleep Time
327.12	Idiopathic Hypersomnia Without Long Sleep Time
327.13	Recurrent Hypersomnia
327.14	Hypersomnia Due To Medical Condition
327.15	Hypersomnia Due To Mental Disorder
327.19	Other Organic Hypersomnia
327.2	Organic Sleep Apnea, Unspecified
327.21	Primary Central Sleep Apnea
327.22	High Altitude Periodic Breathing
327.23	Obstructive Sleep Apnea (Adult)(Pediatric)
327.24	Idiopathic Sleep Related Nonobstructive Alveolar Hypoventilation
327.25	Congenital Central Alveiolar Hypoventilation Syndrome
327.26	Sleep Related Hypoventilation/Hypoxemia In Conditions Classifiable Elsewhere
327.27	Central Sleep Apnea In Conditions Classified Elsewhere
327.29	Other Organic Sleep Apnea
780.5	Sleep Disturbances
780.5	Unspecified Sleep Disturbance
780.51	Insomnia With Sleep Apnea, Unspecified
780.52[a]	Insomnia, Unspecified
780.53	Hypersomnia With Sleep Apnea, Unspecified
780.54	Hypersomnia, Unspecified
780.55	Disruption Of 24-Hour Sleep-Wake Cycle, Unspecified
780.56	Dysfunctions Associated With Sleep Stages Or Arousal From Sleep
780.57	Unspecified Sleep Apnea
780.58	Sleep Related Movement Disorder
780.59	Other Sleep Disturbances
786.09[a]	Other Dyspnea And Respiratory Abnormality

[a] Diagnostic code eliminated in the third iteration of the REP search criteria.

Because these criteria had failed to identify 35.7% of the PAVD participants known to have undergone PSG based on the MSLD, the criteria were modified to be more inclusive. This second iteration of the REP Search Criteria was then submitted as follows: Either a PSG or CPAP procedure code OR one of the same broad, inclusive list a sleep breathing related diagnostic codes from Table 11. That search then identified 690 participants including 229 of the 235 PAVD participants identified in the MSLD, and 443 additional participants that were not in that database or among the 18 participants identified by the first iteration as having had sleep studies or OSA apart from that database. The six participants in the database not identified in the second iteration of the search criteria all had PSGs performed more than 12 years ago and thus may have had their studies coded in a different manner.

An analysis of the specific diagnostic codes leading to the identification of these 690 second iteration participants showed that the number of participants identified in the MSLD by each code compared to the other participants identified by that code varied widely as illustrated in Table 12. Some codes exclusively identified participants known to have had PSGs, whereas other codes identified only participants not found in the MSLD, and other codes identified a mix of MSLD participants and the others.

The ratio of participants with known PSGs to those without known PSGs is one indicator of the relative efficiency of each code in identifying participants that have undergone PSG. A ratio of 1 participant with a known PSG for every 10 participants without a known PSG was arbitrarily selected as a threshold ratio for inclusion of the code in the search criteria. This analysis demonstrates that elimination of four codes

would be predicted to reduce the number of participants identified but not found in the MSLD by 95, while leaving seven participants with PSGs unidentified. Recognize that the seven participants with known PSGs but not identified by the REP criteria did still ultimately contribute to the PSG analysis as they had been identified in the MSLD. Given the 9.5:1 ratio of Mayo to non-Mayo PSGs, the elimination of these codes was predicted to have missed less than one participant with a non-Mayo PSG.

Table 12

Participants Identified by REP Search Criteria, Iteration 2

Code	Participants with a known PSG *n*	Participants without a known PSG *n*	Ratio of participants with known PSGs to those without a known PSG
93.9 [a]	0	1	0.00
327.23	3	0	[b]
780.5	2	9	0.22
780.51	1	0	[b]
780.52 [a]	2	31	0.06
780.53	1	0	[b]
780.57	10	3	3.33
786.09 [a]	5	58	0.09
7735110	17	153	0.11
7735111	9	52	0.17
7735112 [a]	0	5	0.00
7735113	5	38	0.13
7735115	1	2	0.50
7735120	1	9	0.11
7735132	1	2	0.50
7781510	1	0	[b]
7781521	1	0	[b]
7782410	1	5	0.20
7782411	177	62	2.85
7782412	6	8	0.75
34199754	3	5	0.60
Total	247	443	

[a] diagnostic codes eliminated for iteration 3

[b] ratio cannot be calculated as it involves division by zero

Thus, a third iteration of the REP search criteria is as follows: Either a PSG or CPAP procedure code OR one of a shorter, but still inclusive list a sleep breathing related diagnostic codes. This iteration of the search criteria identified a total of 608 participants from the 2,042 that had participated in PAVD round one including the same 229 identified in the second iteration from the MSLD, and the 18 participants previously recognized as having had PSG at the Olmstead Medical Center in the first iteration of the search criteria. This reduction of the number of participants identified in iteration three effectively reduced the number of participants outside of the MSLD by 81 to 362. Based on the analysis above it appears unlikely that a further modification of these search criteria will substantively affect the efficiency of participant identification.

The roster generated by iteration three then represents the PAVD participants identified by the REP search as likely having had PSG and carrying an OSA diagnosis. In the proposed study these participants' linked records were reviewed to verify the performance of PSG, identify the facility at which it was performed and extract the date(s) of testing, quantitative and narrative diagnostic results from the PSG, and available information regarding the OSA therapies recommended. When available any references to patients' current adherence to the recommended therapy was also abstracted from the records.

To validate this REP search method and these final criteria, a random sample of 50 participants not identified as having had PSG or an OSA diagnosis were also manually reviewed. As described in chapter 4, that sample indicated that less than 6% of participants ($n<3$) not identified by the REP search method actually had PSGs or carried a

sleep-related diagnosis, thus these search criteria were accepted, having identified 95% or more of PAVD participants undergoing PSG or having a sleep breathing related diagnosis.

Data Collection and Analysis

Existing PAVD data including the demographic parameters and many of the clinical parameters to be used in this proposed study are maintained by the PAVD data management staff in an electronic format based on standard research procedures for the Mayo Clinic. The author of this study completed and maintained the necessary ethics training for Mayo Clinic and REP research, and had obtained IRB approval for the research at both the Mayo Clinic and the Olmsted Medical Center. Thus, the author had the necessary institutional approvals to access this data and carryout the proposed research. In addition, the author had obtained the approval of the Walden University IRB to carry out the analysis of this data once collected.

The REP search criteria were developed in cooperation with a REP data analyst/programmer who then wrote the script that implements the search using the REP electronic resources. The REP data analyst/programmer then provided an electronic spreadsheet roster of the participants identified by the search with additional associated data fields appropriate to chart review and analysis (Erickson et al., 2007).

Chart review and data collection

Using this electronic roster of participants meeting the REP search criteria a systematic review of participant records was done. The first step was to use the electronic REP browser to identify the types and location of records available for each patient. This

browser allows electronic access to listings of the medical procedure billing and diagnostic codes searched and scanned records that are archived by the REP. Manual review of these codes allowed the identification of the dates, type of records, and locations likely to provide the details of the PSGs performed and the final sleep-related breathing clinical diagnosis and treatment (Erickson et al., 2007).

Once the dates and location of these records were identified the next step was accessing and reviewing those records. For those records maintained in an electronic medical record, the necessary information was abstracted directly from these records. If the necessary records were maintained in a paper only format, the investigator provided a roster of these records to the REP research study assistant who then organized the collection of these paper charts at the appropriate institutional site and scheduled a time for the investigator to visit that record department for the abstracting review (Erickson et al., 2007).

The record review focused on the PSG report, clinical notes that led to the ordering of the PSG, clinical notes subsequent to the PSG in which a sleep-related treatment had been ordered, and more recent notes that provided indications of current adherence to the currently prescribed sleep-related treatment. In addition, where a PSG report or other definitive descriptions of sleep-related evaluations and treatments were not available, a general review of the record was carried out to determine the basis for the record's identification by the REP search criteria.

For this study the following data were then abstracted into an electronic abstraction record: (a) date and location of all PSGs performed; (b) PSG reported

parameters including the AHI or RDI, oxygen saturation nadir, portion of sleep time with oxygen saturation less than 90%, oxygen desaturation index, the central and obstructive AHIs, and total sleep time, (c) the clinical diagnosis from the narrative PSG report; (d) the sleep-related prescription recommended to the patient following the PSG; (e) narrative indications of the patient's subsequent and current adherence to that therapy; and (f) a description of the dates and locations of the records reviewed. This abstraction record was maintained on a laptop computer to allow use at the multiple locations at which charts must be reviewed. The electronic abstraction record was a password protected file that is electronically regularly backed up.

At the conclusion of the abstraction the abstraction file was reviewed for consistency of data with corrections made as indicated noting that the original patient records remained available if needed to clarify inconsistencies.

Analysis

The analysis of the data obtained was approved by the Walden University IRB and was carried out in several stages. The first stage was designed to provide assurance of the validity of the REP search criteria for the identification of at least 95% those with PSGs and clinically diagnosed OSA. As described above, this involved the review of 50 randomly selected patient records not identified by the REP criteria for participants that had completed round one of PAVD. If there were three or more participants (≥6%) from this sample of 50, the search criteria would have been reevaluated based on the characteristics of those additional participants with PSG or OSA-related diagnoses. Since there were two or fewer participants in this sample with a PSG or OSA-related diagnosis

the criteria were accepted as having effectively identified 95% or more of those in the PAVD study that have had PSG or an OSA-related diagnosis.

The second stage of the analysis was to determine if there was evidence of participation bias by comparing those participating in round two with those from round one that did not participate. Similar to the earlier evaluation for participation bias in round one (Jacobsen et al., 2004), this analysis included age, gender, marital status, educational attainment, BMI, history of cardiovascular diseases including coronary artery disease, congestive heart failure, hypertension, history of atrial fibrillation, other cardiovascular disease, diabetes, chronic obstructive pulmonary disease, and history of clinical PSG or diagnosis OSA. Descriptive statistics were tabulated for these participant characteristics in round two participants and nonparticipants stratified by age and gender. For categorical variables statistical comparison was by chi-square test whereas continuous and ordinal variables were compared using the Student t-test. The participation bias found was acknowledged in interpretation of the study's results.

Stage three of the analysis addressed the subtle difference in the scoring algorithm used in a BQ validation study previously done in our institution (Gami et al., 2004) compared to the original validation study (Netzer et al., 1999; "Reprinting of the Berlin Questionnaire," 2000). Table 3 illustrates that the scoring of item one in the questionnaire varied from the original scoring algorithm. Thus, analysis of the resulting difference, if any, in the population prevalence of OSA by the BQ proxy was performed to determine the impact of this difference.

Once the first three stages of analysis were completed, the fourth stage involved a descriptive analysis of the participants with and without clinically diagnosed OSA among those with the OSA proxy based the modified BQ. This descriptive analysis included demographic factors such as gender, age, educational attainment, and marital status. In addition clinical factors previously recorded for the PAVD study were assessed, including BMI, change in BMI from round one to round two, a history of coronary artery disease, congestive heart failure, hypertension, atrial fibrillation, cerebral vascular accident (CVA), diabetes, chronic lung disease, and a cardiovascular disease composite, systolic and diastolic myocardial function, and lipid profile. For continuous variables mean, median, and standard deviation will be reported, and where appropriate continuous variables were analyzed in categorical groups. For example, BMI was considered categorically in normal, overweight, and obese groups in addition to a comparison of means. Since many of these variables were collected in both round one and round two, the more recent round two data was generally used, and an analysis based on the changes of relevant parameters from round one to round two was also performed.

Based on these bivariate analyses factors statistically associated with clinical recognition of OSA were entered in a multiple logistic regression analysis to identify factors that independently predicted the clinical diagnosis of OSA among those with the BQ OSA proxy after adjustment for other variables. The dependent variable was the presence or absence of clinically diagnosed OSA among those with OSA based on the BQ. The regression analysis proceeded with a stepwise, backward strategy. Those factors from the bivariate analysis with a statistically significant difference ($p \leq 0.05$)

between those clinically recognized and unrecognized were all included in the regression model initially. Independent variables that then had insignificant coefficients ($p>0.05$) were the removed from the model one at a time starting with the variable with the highest *p*-value. This process was continued until all of the variables remaining in the model were significant. The final model then had identified the factors that are statistically independent predictors of clinical recognition of OSA among those with OSA based on the BQ proxy.

The results of this analysis were then used to formulate strategies to better recognize those most likely to have undiagnosed OSA. The prevalence of clinically recognized OSA among those with the BQ OSA proxy were also determined and compared to that previously reported in population-based studies using 1990s data (Kapur et al., 2002; Young, Evans et al., 1997).

Protection of Participants Rights

Prior to participation participants in the PAVD study completed a consent form approved by the Institutional Review Boards of both the Mayo Clinic and Olmstead Medical Center. That document includes a detailed description of the nature of the study, risks, and benefits of participation, the opportunity to withdraw from the study, and provides participants the opportunity to authorize investigators to review personal health records for relevant study information. In addition, patients obtaining healthcare from the Mayo Clinic and the Olmsted Medical Center have the opportunity to provide general permission for review of their records for research purposes when they seek routine care at these institutions. Patients who choose not to grant that permission have their clinical

identification numbers censored in the REP browser, and thus their records are inaccessible to review (Erickson et al., 2007). Thus, both the informed consent process within the PAVD study, and the routine consent process in obtaining care in Olmsted County provided mechanisms to protect participant rights for this study.

All of the round two PAVD data, along with data previously obtained in round one of the PAVD study are maintained by the PAVD data management staff in a secure electronic format with appropriate electronic and paper data backup by standard research procedures for the Mayo Clinic. Those with appropriate research ethics training and Mayo Institutional Review Board (IRB) approval for specific PAVD research projects may have access to this data within the limits of their IRB approved research role. This allows for investigators to obtain a working data extract, typically in a standard spreadsheet or statistical analysis software format, from the primary, secure database for the approved project (Erickson et al., 2007). In addition, projects utilizing REP resources must have IRB approval from the Olmsted Medical Center, the other primary REP institutional partner, in order to access those REP resources. The author of this study had completed and maintains the necessary ethics training for Mayo Clinic and REP research. In addition, the author had submitted and obtained IRB approval for the research at both the Mayo Clinic and the Olmsted Medical Center. Finally the author had obtained approval of the Walden University IRB for the plan to analyze this data. Thus, the author had the necessary institutional approvals to access this data and carryout the research. Since the data collected by this study is the property of the larger PAVD study, at the

study's conclusion it will be submitted to the PAVD data management staff to be permanently archived with the rest of the PAVD data.

Summary

This study built on the longitudinal, population-based PAVD study of adults who were age 45 and older on January 1, 1997 to assess the prevalence of clinically recognized OSA in the population. In the second round of that study participants completed the modified BQ which classified participants' risk of OSA as high or low, and was used as a proxy for OSA. Using the resources of the REP, PAVD participants from both rounds one and two with clinically recognized OSA were identified using billing codes for PSG and CPAP along with a group of diagnostic codes for sleep-related breathing diagnoses. The charts of identified participants were reviewed to abstract parameters measured in the clinical PSG, the clinical diagnosis of OSA, and, where possible, any OSA treatment recommended and the participants' adherence to that treatment was also abstracted.

A preliminary analysis of the BQ responses demonstrated that a total of 527 of the original 1,402 participants in round two were at high risk for OSA including 199 women and 328 men. Thus, the study was powered at 80% to detect increases in clinical recognition of 13.3% among men, 17.1% among women, and 4.5 – 10.5% in a mixed gender populations compared to the two previous population based assessments of OSA clinical recognition (Kapur et al., 2002; Young, Evans et al., 1997).

The study's analysis included a validation analysis to assess the effectiveness of the REP search criteria used to identify participants with the clinical diagnosis of OSA by

reviewing 50 randomly selected charts not selected by these criteria. The possibility of participation bias was considered by an analysis comparing the baseline characteristics and the clinical diagnoses of OSA for participants that participated in the round two with those that chose not to participate. A descriptive analysis determined the prevalence of clinically recognized OSA among those with a high risk of OSA based on the BQ. Finally both bivariate and multivariate analyses of factors predictive of OSA clinical recognition were performed.

The study protected participants' rights through a careful informed consent process that was a part of the PAVD study and when participants were provided opportunity to consent the to use of their clinical records in the course of obtaining routine medical care in Olmsted County.

CHAPTER 4: RESULTS

Introduction

This study utilized the community-based sample established in 1997 for the ongoing Prevalence of Asymptomatic Ventricular Dysfunction (PAVD) Study to evaluate the prevalence of clinically recognized obstructive sleep apnea (OSA) among those at high risk for OSA (Redfield et al., 2003). The survey completed by PAVD participants in round two included a modified BQ which was used to predict which participants were at high risk for OSA (Netzer et al., 1999; "Reprinting of the Berlin Questionnaire," 2000). To identify participants with clinically recognized OSA the resources of the REP (Melton, 1996) were used to ascertain those participants' medical records containing one of the sleep-related diagnosis and procedure codes in Table 12. The records of these participants were then reviewed to obtain information about any clinical PSG the participant had undergone and the clinical diagnosis of OSA.

The responses to the BQ items and a host of demographic and clinical parameters had been collected by the PAVD study in Round 1 and/or Round 2. These data points had been electronically archived by study staff that then provided a data extract of the relevant data for this study. The REP search for sleep-related procedure and diagnosis codes was carried out in October 2008 and identified 609 participants. The medical records of these participants were systematically reviewed recording PSG and OSA-related parameters. To validate the REP code search process an additional 50 participants not selected by that process were randomly selected and manually reviewed for evidence of a clinical PSG testing or OSA diagnosis. Data from the REP identified charts that were

reviewed, the 50 participant validation study, the BQ responses, and other relevant fields from the archived PAVD study were then merged to form a single data set used for this study. Coded responses from the BQ were placed in an electronic algorithm to rate participants' OSA risk based on the method of the original BQ validation study as modified for application in this setting(Netzer et al., 1999; "Reprinting of the Berlin Questionnaire," 2000).

The research questions this study sought to answer were the following:

1. What proportion of those at high risk for OSA based on the Berlin Questionnaire (BQ) have been clinically evaluated for OSA?
2. What is the prevalence of clinically diagnosed OSA among those at high risk for OSA based on responses to the Berlin Questionnaire?
3. Has the prevalence of clinically diagnosed OSA increased in the past decade?
4. What factors are predictive of the clinical diagnosis of OSA among those at high risk of OSA?

The data analysis for this study was carried out in the following four stages:

1. Validation of the diagnostic and procedure codes in Table 12 for the identification of clinically recognized OSA by the manual review of 50 randomly selected records not selected by these codes.
2. Participation bias analysis comparing those participating in round two of the PAVD study with those from round one who did not participate, and a descriptive analysis of the resulting sample.

3. Analysis of OSA risk based on the Berlin Questionnaire and the impact of the Berlin Questionnaire scoring modifications used in this study.
4. A descriptive, bivariate, and multivariate analysis of those with clinically recognized OSA in order to identify factors predictive of clinical recognition.

The purpose of stages one through three is to validate the method used to identify those with clinically recognized OSA, and to assess for bias in the data sets used. Thus, these analyses are presented first. Subsequently, the research questions are addressed following the presentation of results for the fourth analytic stage.

Validation of the REP Codes Used for Identification of OSA Clinical Recognition

As described in chapter 3 sleep-related clinical diagnostic and procedure codes were compiled to electronically identify all participants with clinically recognized OSA. Through an iterative process using a database of known sleep studies the diagnostic and procedure codes were refined to efficiently identify all those with PSGs and OSA without selecting those with other sleep-related diagnoses. The collection of codes used was from iteration three (Table 12). Note that three codes in this table labeled with an asterisk (*) were eliminated for iteration three and thus, from this study.

The search for PAVD round one participants with sleep-related diagnoses was carried out in October 2008 using iteration three codes as noted in Table 12. The medical records of the 608 identified participants were reviewed beginning after final approval of the dissertation proposal in April 2009 with these reviews completed in early March 2010. To validate this set of search codes to assure that at least 95% of participants with PSGs and/or OSA were identified by this process a random sample of 50 participants not

selected by iteration three codes was drawn in February 2010 and manually reviewed for evidence of PSG treatment or an OSA-related diagnosis. This review, completed in March 2010, identified a total of four of these 50 randomly selected participants with a sleep-related diagnosis as illustrated in Table 13.

Table 13

Sleep-Related Diagnoses Found in the 50 Participant Validation Sample

Sleep-related diagnosis	Diagnostic Date	AHI by PSG[a]	Treatment
Periodic leg movements of sleep	January 9, 2008	2	Iron supplementation
Mild OSA	November 8, 2008	9	CPAP
Insomnia	January 27, 2009	No PSG	Sleep medication
Insomnia	January 4, 2010	No PSG	Sleep medication

[a] AHI by PSG: apnea-hypopnea index (AHI) by polysomnography (PSG)

Only one participant with clinically recognized OSA was identified, and that clinical diagnosis was not made until after the REP search was carried out. There were also two participants with other, nonOSA sleep-related diagnoses that were made after the REP search was performed. In addition, there was one participant that had a sleep-related diagnosis not related to OSA that was made on January 9, 2008, prior to the REP search. A review by REP staff indicates that this diagnosis was not identified by the search because it is likely that the January diagnosis and procedure codes had not yet been processed into the REP database when the search was carried out in October of 2008 (S. Schrage, personal communication, May 3, 2010).

Thus, in this validation sample there were no participants with clinically recognized OSA prior to the date of the search that were not identified by the iteration three collection of diagnostic and procedure codes. With one participant identified in this 50 participant sample with a nonOSA sleep-related diagnosis there is an estimated 2%

chance that these criteria would not detect a participant with a sleep-related diagnosis which, in the entire study sample, could include some participants with OSA. Since those with OSA represent a subset of those with any sleep-related diagnosis, the chance of this REP search method having failed to identify a participant with OSA is estimated to be less than 2%. Therefore, this validation analysis confirms that these criteria identified at least 95% of those with clinically recognized OSA in the PAVD sample.

Round Two Participation Bias and Descriptive Analysis of the Sample

This study was carried out using the population-based community sample established for the PAVD study as previously described in chapter 2 (Ammar et al., 2006; Redfield et al., 2003). The primary study using this database had been based on echocardiographic endpoints. Thus, previous analyses used only participants that had completed an echocardiogram, which in Round 1 and 2 included 2,042 and 1,402 participants, respectively. Further review of the archived PAVD data revealed that there were an additional five participants that were invited to participate in Round 2 despite not having completed the Round 1 echocardiogram. In addition, in Round 2 there were an additional 15 participants that had completed the Berlin Questionnaire but did not complete the Round 2 echocardiogram. Because these additional participants had completed the essential elements for the present study, they have been included in the analyses which follow giving 2,047 participants in Round 1 and 1,417 participants in Round 2. The age and gender characteristics of these samples are described in Table 14.

Overall there was a nearly 70% participation rate from Round 1 to Round 2. Similar to a previously reported participation analysis for Round 1 (Jacobsen et al., 2004), there was a somewhat lower Round 2 participation rate for the youngest age group, and a substantially lower participation rate for the oldest group in both genders. In addition, similar to that early analysis, there was a somewhat higher participation rate for men compared to women. Thus, the subsequent bivariate analyses of participation are age- and gender-adjusted to the population participating in Round 1.

Table 14

Round 2 Participation Rate by Age and Gender

Gender & Round 1 Age (yrs)	Round 1 Participants (n)	Round 2 Participants (n)	Participation Rate (%)	95% CI
Overall	2047	1417	69.2	67.2-71.2
Women	1061	714	67.3	64.5-70.1
45-54	302	220	72.9	67.9-77.9
55-64	312	243	77.9	73.3-82.5
65-74	264	278	67.4	61.7-73.1
75+	183	73	39.9	32.8-47.0
Men	986	703	71.3	68.5-74.1
45-54	299	224	74.9	70.0-79.8
55-64	315	245	77.8	73.2-82.4
65-74	257	185	72.0	66.5-77.5
75+	115	49	42.6	33.6-51.6

Participation bias analysis for the initial Round 1 sample (Jacobsen et al., 2004) had considered a number of demographic and disease history factors as potentially associated with Round 1 participation. A similar analysis for Round 2 participation is presented in Table 15. In this bivariate analysis there was a statistically significant underrepresentation of those with noncoronary artery disease cardiovascular disease (nonCAD CV disease), congestive heart failure (CHF), any cardiovascular disease,

chronic obstructive pulmonary disease (COPD), those with no more than a high school education, and a higher Charlson Comorbidity Index weighted for age and severity (Charlson, Pompei, Ales, & MacKenzie, 1987). Relevant to the present study there was no statistically significant difference in Round 2 participation after age and gender adjustment related to BMI, having undergone a clinical PSG, or the clinical diagnosis of OSA.

Table 15

Participation Rate by Disease History and Demographic Characteristics with Age and Gender Adjustment

	Condition at round 1 (n)	Round 2 participants (n)	Participation rate (%)	Age & gender adjusted participation rate (%)[a]	*p* [b]
Coronary artery disease					
Present	248	143	57.7	65.5	0.093
Absent	1799	1274	70.8	70.1	
NonCAD CV disease					
Present	515	290	56.3	63.2	<0.0001 [c]
Absent	1532	1127	73.6	72.2	
Atrial fibrillation/flutter					
Present	100	48	48.0	61.5	0.202
Absent	1947	1369	70.3	69.9	
CHF					
Present	45	16	35.6	55.6	0.0006 [c]
Absent	2002	1401	70.0	69.7	
Hypertension					
Present	561	352	62.7	66.5	0.074
Absent	1486	1065	71.7	70.8	
Any cardiovascular disease					
Present	550	316	57.5	64.1	0.0002 [c]
Absent	1497	1101	73.5	72.1	
COPD					
Present	94	39	41.5	45.8	0.001 [c]
Absent	1953	1378	70.6	70.3	
Diabetes mellitus					
Present	153	92	60.1	63.5	0.072
Absent	1894	1325	70.0	69.8	
Marital Status					
Currently married	1588	1138	71.7	70.0	0.227
Not currently married	447	273	67.0	67.0	
Education					
At least some college	1154	868	75.2	74.5	<0.0001 [c]
No more than high school	759	466	61.4	63.1	
Race/Ethnicity					
Caucasian, non-Hispanic	1996	1385	69.4	69.4	0.487
Non-Caucasian or Hispanic	51	32	62.7	64.8	
Charlson Index, Weighted					
0	259	204	78.8	82.5	
1-2	912	689	75.5	69.6	<0.0001 [c]
≥3	871	522	59.9	64.2	

(table continues)

		Condition at round 1 (n)	Round 2 participants (n)	Participa-tion rate (%)	Age & gender adjusted participa-tion rate (%)[a]	*p* [b]
BMI						
	<20	49	34	69.4	67.6	0.320
	20 – 24	466	318	68.2	68.3	
	25 – 29	869	617	71.0	70.9	
	30+	662	448	67.7	66.5	
Clinical PSG						
	Performed	280	204	72.9	70.4	0.636
	Not performed	1767	1213	68.6	69.0	
Clinical OSA						
	Diagnosed	270	197	73.0	70.9	0.505
	No diagnosis	1777	1220	68.7	68.9	

[a] Age and gender adjustments are to the standard of the Round 1 participating population. [b] *p* values are for the Chi square Likelihood Ratio. [c] Parameter considered statistically significant and retained in the initial multivariate logistic regression.

A multivariate logistic regression analysis comparing those from Round 1 that participated in Round 2 with those who did not participate was performed initially using only the conditions identified as statistically significant in the bivariate analysis in Table 15. Age and gender were also included since participation rates had been adjusted for these factors in Table 15. In this model the continuous variable age was represented by an ordinal variable, categorized as shown in Table 14. In a stepwise manner, factors with coefficient *p* values greater than 0.05 were removed from the model. All of the age group variables were retained in the model despite the fact that the 65 – 74 year old age group was not statistically different from the reference group (45 – 54 years old) because of the lower participation rates in younger and older age groups. When considering the cardiovascular disease related variables with the other variables in the model only nonCAD CV disease ultimately remained statistically significant. The Charlson Comorbidity Index, which summarizes in a single variable comorbidity from spectrum of chronic disease, appears to be a better predictor of participation in this regression analysis than many of the individual chronic diseases included in this index (Charlson et al., 1987). The unadjusted and adjusted odds ratios with 95% confidence intervals are presented for the variables retained in the final model in Table 16.

Table 16

Odds Ratios for Logistic Regression Analysis of Factors Predicting Round 2 Participation

	Unadjusted OR [b]	Adjusted OR [c]	Adj. OR 95% CI
Age Group, years			
45-54 [a]	1	1	
55-64	1.24	1.57	1.170 – 2.102
65-74	0.81	1.31	0.941 – 1.832
75+	0.25	0.45	0.306 – 0.666
Gender			
Female [a]	1	1	
Male	1.21	1.24	1.002 – 1.525
Education			
At least some college [a]	1	1	
No more than high school	0.52	0.59	0.475 – 0.727
COPD			
Absent [a]	1	1	
Present	0.30	0.40	0.250 – 0.645
NonCAD CV disease			
Absent [a]	1	1	
Present	0.46	0.67	0.528 – 0.862
Charlson Index			
<3 [a]	1	1	
3+	0.47	0.73	0.559 – 0.965

Note. Only variables retained in the final logistic regression model are presented.

[a] Reference category. [b] Unadjusted OR based on bivariate analysis prior to age and gender adjustment. [c] Adjusted OR from the final logistic regression model including only the listed factors.

This analysis indicates that those with COPD, nonCAD CV disease, and those with greater comorbidities as measured by the Charlson Index, were under-represented as participants in Round 2. Since participation in Round 2 involved completion of a survey and coming to the research clinic for physical examination and an echocardiogram, it is not unreasonable that those with a greater disease burden might have found it more difficult to participate in Round 2. The younger, 45 – 54 year old age group was under-represented compared to the 55 – 64 year old age group, likely because this group

probably had a greater proportion that were employed on a full time basis making the scheduling of Round 2 participation more challenging. Again the groups older than the 55 – 64 year old group were comparatively under-represented likely due to difficulties in being able to participate in the study. Those better educated had a higher participation rate possibly on the basis of their having a greater interest in research participation. Men were also somewhat over represented, though note that the confidence interval nearly includes one.

In an earlier analysis of participation bias in Round 1 of the PAVD study (Jacobsen et al., 2004) a similar group of factors had been analyzed, but there only age, COPD, and education demonstrated a statistically significant differential in participation. The direction of these earlier participation differentials was the same as that in the present analysis. Thus, it is important to recognize that in Round 2 these factors will be even more divergent from the original population-based sample from which Round 1 had been drawn. These differences from the population at large have been acknowledged in the interpretation of the study results. However, relevant to endpoints of the present study, as presented in Table 15 there was no statistically significant difference in participation related to BMI, having undergone clinical PSG, or having a clinical OSA diagnosis.

This study then considers the resulting PAVD round 2 sample of 1,417 participants. Tables 17 and 18 provide a descriptive analysis of this sample related to continuous and categorical variables, respectively. An analysis of gender differences in the sample is also presented.

Table 17

Descriptive Analysis of PAVD Round 2 Participants (n=1,417 including 49.6% males) with Gender Comparison for Continuous Variables

	n[a]	mean	median	standard deviation	mean (male)	mean (female)	p[b]
Age, round 2 (years)	1417	65.2	64.0	9.6	64.9	65.4	0.33
Education, round 2 (years)	1373	14.3	14	2.6	14.6	14.0	<0.0001
BMI, round 1	1417	28.3	27.6	5.1	28.9	27.7	<0.0001
BMI, round 2	1417	28.5	27.9	5.1	29.1	28.0	<0.0001
BMI difference, round 2 – round 1	1417	0.24	0.29	1.9	0.24	0.25	0.94
Echocardiographic characteristics, round 2							
Ejection fraction (%)	1073	65.7	66.3	7.7	63.8	67.3	<0.0001
Left atrial volume index (ml/m^2)	1364	24.7	23.4	8.5	25.7	23.7	<0.0001
Lipid Profile, round 1							
Total cholesterol (mg/dl)	1411	203.1	201.0	34.2	196.4	209.7	<0.0001
Triglycerides (mg/dl)	1413	145.1	126.0	80.1	147.7	142.5	0.22
High density lipoprotein (HDL) (mg/dl)	1411	46.1	44.0	14.2	39.5	52.6	<0.0001
Low density lipoprotein (LDL) (mg/dl)	1411	128.0	127.0	31.4	127.3	128.6	0.45
Charlson Index, round 2	1402	3.27	3.0	2.53	3.51	3.05	0.0006
Biometric measurements, round 2							
Hip circumference (cm)	1416	104.1	103.0	9.8	104.4	103.9	0.39
Neck circumference (cm)	1415	37.3	37.0	4.3	40.4	34.3	<0.0001
Waist circumference (cm)	1416	92.2	92.0	14.9	100.2	84.4	<0.0001
Waist-Hip Ratio	1416	0.884	0.889	0.102	0.959	0.810	<0.0001

[a] Number of participants with data for variable. [b] Student t-test for difference of gender means.

Table 18

Descriptive Analysis of PAVD Round 2 Participants (n=1417 including 49.6% males) with Gender Comparison for Categorical Variables

Variable	*n*[a]	%[b]	male %[c]	female %[c]	*p*[d]
Marital status (married vs not-married)	1416	79.1	87.3	71.0	0.04
Education (at least some college vs ≤high school)	1380	65.1	66.7	63.6	0.22
Race/ethnicity (Caucasian, non-Hispanic vs other)	1417	97.7	97.4	98.0	0.44
Atrial fibrillation or Atrial flutter	1417	5.9	7.4	4.3	0.01
Coronary artery disease (CAD)	1417	15.0	23.6	6.6	<0.0001
NonCAD cardiovascular disease	1264	38.3	39.8	36.7	0.26
Any cardiovascular disease	1266	40.8	43.9	37.5	0.02
Congestive heart failure	1417	2.2	2.8	1.5	0.09
COPD	1223	7.1	8.8	5.4	0.02
Cerebral vascular accident	1220	3.4	3.4	3.3	0.90
Hypertension	1417	42.6	42.5	42.7	0.94
Diabetes mellitus, Type 2	1234	11.8	15.7	7.9	<0.0001
REP search identified	1417	29.4	32.1	26.8	0.03
Clinically diagnosed OSA[e]	1417	13.5	19.8	7.4	<0.0001
Clinical testing by PSG [e]	1417	14.4	20.5	8.4	<0.0001

[a] Number of participants with data for variable. [b] Percentage with the first of the two dichotomous choices listed with the variable; for medical disorders and testing, percentage having the disorder or test. [c] The proportion of male and female round 2 participants with the first of the two dichotomous choices, the disorder or test. [d] *p*-value for Chi Square Likelihood Ratio comparing genders. [e] Based on the validation analysis presented in Table 13 (and following) the OSA and PSG status for all participants is presumed to have been ascertained.

The mean age of the round 2 sample was 65.2 ± 9.6 years and a median of 64 years as illustrated in Table 17. This is 2.4 years older than the original round 1 mean age; however, the mean age difference from round 1 to round 2 for round 2 participants was 4.03 years, consistent with the original study's designed four year follow up (Redfield et al., 2003). Round 2 females were slightly but not significantly older than males. As a socioeconomic marker, education was evaluated using both the continuous variable, total years of education (Table 17), and as dichotomous variable (Table 18)

comparing those with no more than a high school education with those having at least some college. Education levels when compared by gender using the dichotomous variable were not significantly different; however, using the continuous variable the mean 0.6 year difference was highly significant statistically. A large majority, 79.1%, of the sample was currently married with men statistically more likely to be married (87.3%) than women (71.0%). The race/ethnicity dichotomous variable considered participants as either, Caucasian, non-Hispanic, or other, and demonstrated this sample to be quite homogeneous with 97.7% of the sample identified as Caucasian, non-Hispanic. As table 15 illustrates there was no statistical difference with regard to race and ethnicity from round 1 to round 2. However, the original round 1 sample and the round 2 sample do over represent this racial and ethnic category since U.S. Census Bureau data (US Census Bureau, 2010) indicate that Olmsted County was 95.3% and 89.0% Caucasian, non-Hispanic in 1990 and 2000, respectively. Thus, this study's result should not be extrapolated to non-Caucasian and Hispanic populations.

Analysis of obesity in the sample demonstrates that the BMI for the round 2 participants had significantly (p<0.0001) increased from round 1 to round 2 (mean BMI 28.5 vs. 28.3), and that men were statistically more obese than women (mean BMI 29.1 vs. 28.0). However, the increases from round 1 to round 2 for men and women were not statistically different (p=0.94). Two echocardiographic characteristics were considered, ejection fraction which is a measure of systolic function, and left atrial volume index, a measure of left atrial size that has been correlated with OSA and atrial fibrillation (Orban et al., 2008; Rodrigues et al., 2009; Toh et al.). In comparing the genders, both of these variables were statistically different. Other biometric measures of body habitus show that

men and women did not differ significantly in hip circumference, whereas there was, as expected, a statistically significant difference in neck and waist circumference as well as waist-hip ratio.

Analysis of clinical variables in Table 18 demonstrates that, in this sample, men were more likely than women to have atrial fibrillation/flutter, CAD, COPD, type 2 diabetes mellitus, and a composite of any cardiovascular disease. This increased morbidity is also illustrated by a statistically higher Charlson Index for men than women (3.51 vs. 3.05). However, there was no statistical difference in the prevalence of cerebrovascular accidents and hypertension between men and women in this sample. Round 2 participants' lipid profile data collected at round 1 demonstrated a higher total cholesterol and HDL cholesterol for women than men with there being no statistical difference between the genders for triglyceride and LDL cholesterol levels.

As described in more detail in Table 22, chart review found 204 (14.4%) of round 2 participants had undergone a clinical PSG and that 197 (13.5%) had clinically diagnosed OSA. Men were 2.68 times more likely to have clinically diagnosed OSA than women, and 2.44 times more likely have undergone PSG with both of these differences statistically significant ($p<0.0001$).

In summary, the round 2 sample was relatively gender balanced, with a mean age of 65.2 years. Multivariate participation bias analysis from round 1 to round 2 demonstrates underrepresentation of the youngest and oldest, women, those less educated, and those with co-morbidities generally based on the Charlson Index, and specifically related to COPD and nonCAD cardiovascular disease. There were a number of gender differences with men being more obese, having greater morbidity related to

atrial fibrillation/flutter, CAD, COPD, type 2 diabetes mellitus, and a composite any cardiovascular disease measure. Men were also far more likely to have undergone PSG and to be diagnosed with OSA.

OSA Risk by BQ, Analysis of Scoring Modification, and Diagnostic Performance

The round two survey for the PAVD study had included questions for the modified BQ with participants' responses having been coded in the PAVD database. For this study the BQ responses were among the fields extracted from that database and ultimately merged with the clinical chart review data for analysis in this study. The BQ responses were scored based on the originally validated algorithm (Netzer et al., 1999; "Reprinting of the Berlin Questionnaire," 2000) and OSA risk classifications were assigned. In round two 705 (49.8%) participants were at high risk for OSA as demonstrated in Table 19 which also includes age and gender specific prevalence rate for this population.

Table 19

BQ OSA Risk & Prevalence by Age and Gender

Gender, round 2 Age (yrs)	OSA risk by BQ, Netzer scoring algorithm ("Reprinting of the Berlin Questionnaire," 2000)				
	Low	High	Total	Prevalence %	(95% CI)
Overall	712	705	1417	49.8	(47.2 - 52.4)
Women	416	298	714	41.7	(38.1 – 45.3)
45-54	66	42	108	38.9	(29.7 – 48.1)
55-64	158	112	270	41.5	(35.6 – 47.4)
65-74	117	91	208	43.8	(37.1 – 50.5)
75+	75	53	128	41.4	(32.9 – 49.9)
Men	296	407	703	57.9	(54.3 – 61.5)
45-54	60	71	131	54.2	(45.7 – 62.7)
55-64	97	144	241	59.8	(53.6 – 66.0)
65-74	88	130	218	59.6	(53.1 – 66.1)
75+	51	62	113	54.9	(45.7 – 64.1)

These prevalence rates are substantially higher than those reported in the literature as summarized in Table 1. A previous application of the BQ to assess prevalence had indicated gender specific rates of 37.9% and 27.8% for men and women, respectively, from a nonpopulation-based sample in Cleveland, Ohio (Netzer et al., 2003). The previous study (Redline et al., 2003) that most closely approximates the prevalence noted here was done in a much younger population with a mean age of 32 compared to 65.2 in the present study. The gender differential and increasing prevalence prior to age 65 demonstrated here is also consistent with previous studies as described in Table 1 and elsewhere (Young, Peppard et al., 2002). Thus, based on the application of the BQ in this study it appears that the prevalence of OSA is greater than most prior studies, but follows a pattern otherwise similar to previous studies.

As noted in this study's literature review the wording, use of questions, and the scoring algorithm for the BQ have varied somewhat in applications reported in the literature. In the application of the BQ in this study there were two questions regarding nodding off or falling asleep while driving (Table 3, questions 8 and 9) that were not used due to concerns regarding vicarious liability (A.S. Gami, personal communication, July 17, 2007). Excluding these questions from this application of the BQ while using the same scoring algorithm that was used in the original validation study (Netzer et al., 1999; "Reprinting of the Berlin Questionnaire," 2000) would lead to lower scores in category two (Table 3) and a lower rate of high OSA risk classification for this study compared to the instrument's original application.

Though it is not possible to accurately predict what responses to these questions might have been in this study, 19.0% of the participants responding to this question in the original validation study (Netzer et al., 1999) had reported nodding off or falling asleep while driving (Table 2, p. 488) including 4.4% who reported doing so at least three times weekly. In that study a total of 231 (31.0%) participants had met the scoring threshold for a positive category two.

In the present study there were only 177 (12.7%) participants that were positive in category two. However, among the 1222 participants with a negative category two, 532 (43.5%) were still classified as high risk based on their responses to questions in categories one and three. Had there been a similar portion (31%) with a positive category two, there would have potentially been an additional 18.3% of the sample with a positive category two, though some portion of these would likely have already met the threshold for high risk based on category one and three responses. Thus, it is likely that the

exclusion of questions 8 and 9 from Table 3 in this application of the BQ has underestimated the prevalence of high risk for OSA by no more than about 15%.

An analysis of a difference in the BQ scoring algorithm used previously in our institution also is an example of the impact on overall BQ performance with a difference in the algorithm used for a threshold-based classification system. The first published use of the BQ to assess OSA risk in our institution (Gami et al., 2004) had not scored question one as part of a positive determination for category one in Table 3. That study had validated the BQ based on a subset of 44 patients who had clinical PSGs performed during the course of their care. In this validation set a sensitivity of 86%, specificity of 89%, and a positive predictive value of 97% had been demonstrated. However, the original validation study for the BQ (Netzer et al., 1999; "Reprinting of the Berlin Questionnaire," 2000) had scored question 1 as one of the items included in a positive determination for category one. To evaluate the impact of this variation in scoring algorithm the BQ responses for this study were scored using both algorithms for comparison.

In round two of this study 1417 participants completed the BQ with 1355 responding to question one which had included a “don’t know” response. Of these respondents, 1322 reported knowing their snoring status including 989 indicating that they snored and 333 that reported not snoring. An additional 33 reported not knowing their snoring status. Based on these responses the original scoring algorithm (Netzer et al., 1999; "Reprinting of the Berlin Questionnaire," 2000) would have numerically scored 989 (69.8%) participants differently than the previous application and validation of the instrument in our institution (Gami et al., 2004). However, because the BQ algorithm

places participants in a high risk category based on a threshold in each of three categories, it is possible that these 989 participants met the category one threshold without having question one scored, or met criteria for the high risk classification in categories two and three alone. Thus, additional analysis was carried out to determine the actual impact of this algorithm difference on the BQ OSA risk classification.

This analysis is presented in Table 20. Based on this OSA risk classification comparison for these two algorithms 168 (11.9%) participants were classified as low risk for OSA by the Gami algorithm whereas the Netzer algorithm classified them as high risk. For the 989 (69.8% of the sample) participants that reported snoring that could have led to BQ risk misclassification comparing the Gami and Netzer algorithms, only 168 were ultimately misclassified. Thus, with a threshold-based scoring system a variation in the scoring algorithm does not misclassify all those responding to the items associated with the algorithm variation. Note that, as illustrated in Table 3, this study used the originally validated scoring algorithm for responses to question 1 rather than the Gami algorithm.

Table 20

Comparison of BQ risk classification for Netzer and Gami Scoring Algorithms

BQ score & OSA risk, Gami algorithm	BQ score & OSA risk, Netzer algorithm				Total
	Low risk		High risk		
	0	1	2	3	
Low Risk					
0	166	144	0	0	880
1	0	402	168	0	
High Risk					
2	0	0	442	19	537
3	0	0	0	76	
Total	712		705		1417

This study's REP directed chart review identified 204 participants that had completed the BQ and had undergone clinical PSG testing. Therefore it is possible to construct a PSG-based validation analysis for BQ diagnostic performance in assessing OSA risk. Because the diagnoses made by a clinician evaluating the patient consider a variety of factors in addition to the PSG-based AHI, there was variation between the clinical diagnosis and the AHI-based diagnosis for 27 participants. Table 21 presents two-by-two table analyses of BQ validation and performance for both AHI-based and clinical OSA diagnoses.

Table 21

Validation of the BQ with Diagnostic Performance by Clinical and AHI-Based OSA Diagnoses

	Clinical diagnosis		AHI-based diagnosis		
Risk by BQ	OSA	No OSA	OSA	No OSA	Total
High	148	17	136	29	165
Low	32	7	28	11	39
Total	180	24	164	40	204

	BQ diagnostic performance (95% CI)	
Sensitivity	$\frac{148}{180} = 82.2\%\ (77-88\%)$	$\frac{136}{164} = 82.9\%\ (77-89\%)$
Specificity	$\frac{7}{24} = 29.2\%\ (11-47\%)$	$\frac{11}{40} = 27.5\%\ (14-41\%)$
Positive Predictive Value	$\frac{148}{165} = 89.7\%\ (85-94\%)$	$\frac{136}{165} = 82.4\%\ (77-88\%)$
Negative Predictive Value	$\frac{7}{39} = 17.9\%\ (6-30\%)$	$\frac{11}{39} = 28.2\%\ (14-42\%)$

In previous studies of test validation based in clinical practice test verification bias has been recognized as impacting diagnostic performance in this setting (Roger et al., 1997). In clinical practice, though it is unlikely that the BQ is formally used broadly, clinicians now are likely recognize elements of the BQ as OSA risk factors and pursue PSG for participants likely to have OSA. So it might be expected that those undergoing PSG are more likely to ultimately be found to have OSA. Indeed in round two only a minority, 11.8% - 19.6%, of those undergoing clinical PSG ultimately were found not to have OSA depending on whether a clinical or AHI-based diagnostic criterion was used. Thus, this BQ validation analysis will be less robust with regard to specificity and negative predictive value (NPV), and more robust for sensitivity and positive predictive value (PPV) as is illustrated by the confidence intervals in Table 21.

When comparing the BQ performance in this analysis with the published literature as displayed in Table 3, values for sensitivity and PPV are similar and

sometimes higher, whereas those for specificity and NPV are generally lower. Thus, based on the analysis in this sample with over 80% prevalence of OSA, the BQ appears to be a substantially better instrument to screen for OSA, than it is to rule out OSA. Indeed among those that were at high risk for OSA based on the BQ and were studied by PSG, only 10.3% - 17.6% were ultimately found not to have OSA by clinical and AHI-based diagnostic criteria, respectively. By contrast, for those identified as being at low risk by the BQ a majority, 71.8% - 82.1%, were ultimately found have OSA and represent false negatives by the BQ.

Clinical Recognition of Those with OSA by BQ

As previously described this study used the REP resources to identify participants with diagnostic and procedure codes indicating that a sleep-related diagnosis had been made or PSG had been performed. That process had identified 608 participants from round one of the PAVD study. In addition there were five participants not previously included in round one as an echocardiogram was not completed but that were invited to round two, and 15 additional participants that had completed the round two survey including the BQ but had not completed the round two echocardiogram. In addition, as previously described, 50 round one participants were randomly selected for manual review to validate the REP search criteria. The clinical records for all of these participants were manually reviewed; however, because several these participants were identified for review by more than one of these methods, ultimately there were 666 round one participants' records that underwent review, including 460 round two participants.

Among the 666 round one participants a total of 280 participants were identified with at least one clinical PSG including 204 round two participants. The clinicians caring

for these 204 participants reported a clinical diagnosis of OSA in 180 of these participants, whereas AHI-based criteria for OSA were met in only 164 of these participants. In addition, there were 12 of the 256 round two participants without a PSG for which there was a clinician reported OSA diagnosis based on clinical symptoms, or possibly other diagnostic testing such as overnight oximetry. Combining the clinician reported and AHI-based OSA diagnoses then classified a total of 197 of the 460 participants whose charts were reviewed having clinically recognized OSA. Table 22 tabulates these diagnoses based on the presence of at least one PSG in the available clinical record.

Table 22

Clinician Reported and AHI-Based OSA Diagnoses

Type of OSA diagnosis		PSG	No PSG	Total
Clinician reported	Present	180	12	192
	Absent	24	244	268
AHI-based	Present	164	0	164
	Absent	40	256	256
Clinician reported or AHI-based	Present	185	12	197
	Absent	19	244	263
	Total	204	256	460

Consideration of the data in Table 22 demonstrates that there were five participants for whom AHI-based diagnostic criteria for OSA had been met which were not confirmed by the clinician, 21 clinician reported diagnoses that were not supported by the PSG performed, and 12 diagnoses made without the benefit of PSG. This analysis illustrates that, though the PSG is an important element in the clinical diagnosis of OSA it appears not to represent a sine qua non for OSA. For the purpose of the analyses of the clinical recognition of OSA which follow, these 197 participants recognized by either

clinician reported OSA diagnosis or AHI-based OSA diagnostic criteria will be considered to have been recognized clinically with OSA.

Table 23

Clinical Recognition of OSA in Round two Subjects Considering the BQ's PPV, and NPV

	BQ High Risk (n=705)	BQ Low Risk (n=712)	Total (n=1417)
OSA clinically recognized	160	37	197
Predicted number with OSA based on BQ PPV & NPV (95% CI) [a]	508 (486-529)	292 (271-313)	800 (757-842)
Clinical recognition rate based on predicted number with OSA (95% CI) [b]	31.5% (27.5%-35.5%)	12.7% (8.9%-16.5%	24.6% (21.6%-27.6%)

[a] Table 6, AHI>5 without regard to symptoms: PPV 72%, NPV 59%; 95% CI based on the CI for PPV & NPV from Table 6. [b] 95% CI based on portion recognized from the number predicted to have OSA.

Table 23 demonstrates that 160 of the 705 participants with BQ identified high risk for OSA have been clinically recognized in this sample. This represents 22.7% (95% CI: 20 – 26%) of those at high risk. However, the BQ is known to have a PPV and NPV of less than 100%. Using the PPV and NPV values reported from a pooled analysis based on the 1038 participants in nine published studies in Table 6, a PPV of 72% and a NPV 59% are used to predict the actual number of participants with OSA in the sample in this study. Based on these estimated numbers of participants with OSA in this sample, an estimated 24.6% of those with OSA have been clinically recognized.

Consideration of these confidence intervals demonstrates that the rate of clinical recognition is not significantly different whether assuming a PPV and NPV of 100%, or an actual PPV and NPV from Table 6. In addition, use of the actual PPV and NPV only allows prediction of a number of participants likely to actually have OSA based on the

BQ. It does not allow prediction of the specific participants in high or low BQ risk groups that will actually have OSA. There are also no reliable data regarding the variation of the BQ PPV and NPV by age, gender or other variables germane to the analyses which follow. Therefore, the following analyses will be based on BQ OSA risk without accounting for the PPV and NPV of the instrument.

Bivariate analysis of demographic characteristics potentially associated with clinical recognition is displayed in Table 24. Gender difference is highly predictive (p <0.0001) of clinical recognition with the rate of recognition for males more than twice that for females. Age, considered as a continuous variable, reaches statistical significance (p = 0.043) as a predictor of clinical recognition with those recognized being, on average, 1.7 years younger than those with unrecognized OSA. However, when age is considered as a categorical variable in 10-year increments it is no longer statistically significant in predicting clinical recognition.

Table 24

Bivariate Analysis of Demographic Characteristics and Clinical OSA Recognition

Demographic Characteristic	BQ High Risk (n)	Mean Recognized, Unrecognized	Clinically Recognized (%)	*p*[a]
Gender				
Male	407		29.5	< 0.0001[c]
Female	298		13.4	
Age	705	63.8, 65.5 yrs		0.043 [c]
45-54	113		20.0	
55-64	256		36.9	0.20
65-74	221		31.3	
75+	115		11.9	
Age by Gender				
Male Age	407	63.9, 65.3 yrs		0.19
45-54	71		33.8	
55-64	144		29.9	0.68
65-74	130		29.2	
75+	62		24.2	
Female Age	298	63.4, 65.8 yrs		0.14
45-54	42		19.1	
55-64	112		14.3	0.40
65-74	91		13.2	
75+	53		7.6	
Education[b]	686	14.7, 14.1 yrs		0.015 [c]
At least some college	435		23.7	0.71
No more than high school	254		22.4	
Education by Gender				
Male Education[b]	395	14.8, 14.2 yrs		0.056 [c]
At least some college	255		31.4	0.48
No more than high school	143		28.0	
Female Education[b]	291	13.9, 14.1 yrs		0.58
At least some college	180		12.7	0.54
No more than high school	111		15.3	
Marital Status				
Currently married	568		23.4	0.37
Not currently married	136		19.9	
Marital Status by Gender				
Male				
Currently married	360		30.3	0.36
Not currently married	46		23.9	
Female				
Currently married	208		11.5	0.16
Not currently married	90		17.8	

(table continues)

Note. Totals for analyses are not always equal to sample and gender totals due to missing data for individual variables.

[a] *p*-values represent chi square likelihood ratios for categorical variables and comparison of means and Student t-test for continuous variables. [b] The continuous education variable is total years of educational attainment. [c] Parameter considered statistically significant and retained in the initial multivariate logistic regression.

Because gender was so highly significant in predicting clinical recognition, age, education, and marital status were analyzed both in the total sample and segregated by gender. Years of educational attainment as a continuous variable was predictive of clinical recognition with those recognized having, on average, 0.6 years more education than those with unrecognized OSA. Segregated by gender, years of educational attainment only approached statistical significance for males. When education was dichotomized to at least some college versus no more than a high school education, it was not a significant predictor of clinical recognition. Marital status was not a predictor of clinical OSA recognition in the total sample or when segregated by gender. Among these demographic factors, gender, age, and education appear to be significant predictors of clinical recognition, the latter two variables only when considered as continuous variables.

As previously noted in chapter 2, BMI is a significant OSA risk factor with a one standard deviation difference in BMI increasing the odds of OSA by 55% (Young, Shahar et al., 2002), and a longitudinal weight increase of 10% associated with a 32% increase in OSA severity (Peppard et al., 2000). The standard epidemiology classification

of BMI includes <20 under weight, 20 – 25 normal weight, 25 – 29 overweight, and >30 obese. This classification was used to assign BMI groups in this study for round 1 and round 2.

As a longitudinal study PAVD data allows assessment of clinical recognition based on the BMI at the time of BQ completion (round 2), an average of four years previously (round 1), and based on the change in BMI during this four year interval. The bivariate analysis for these BMI characteristics is presented in Table 25 for the entire sample at high risk of OSA based on the BQ. Note that BMI at either round 1 or round 2 considered as either a continuous or ordinal variable was associated with a statistically significant difference in clinical recognition with those with a higher BMI most likely to be clinically recognized. However, the BMI difference from round 1 to round 2 was only associated with a significant difference in clinical recognition when considered based on the change in BMI group. It appears that those most likely to be clinically recognized were those with the least change in BMI.

Table 25

Bivariate Analysis of BMI Characteristics Comparing Those with Clinically Recognized and Unrecognized OSA Among Those at High BQ Risk

BMI Characteristic	BQ High Risk (n)	Mean Recognized, Unrecognized	Clinically Recognized (%)	*p*[a]
Round 2	705	33.5, 30.0		<0.0001[b]
<20	10		0	
≥20 - <25	89		12.4	<0.0001
≥25 - <30	212		15.6	
≥30	394		29.4	
Round 1	705	33.0, 29.7		<0.0001[b]
<20	11		0	
≥20 - <25	82		14.6	<0.0001
≥25 - <30	253		15.0	
≥30	359		30.6	
Difference, round 2 – round 1	705	0.49, 0.35		0.47
Group difference, round 2 – round 1				
2 group decline	2		0	
1 group decline	48		10.4	0.012[b]
No change in group	573		25.0	
1 group increase	82		14.6	

[a] *p*-values represent chi square likelihood ratios for categorical variables and comparison of means by Student's t-test for continuous variables. [b] Parameter considered statistically significant and retained in the initial multivariate logistic regression model. Where continuous and ordinal variables are both significant only the continuous variable was retained.

As noted above in Table 24 there was a substantial difference in OSA clinical recognition by gender. Thus, gender specific bivariate analyses of BMI characteristics were performed. The *p*-values for these gender specific analyses are summarized in Table 26. Note that the BMI at either round 1 or 2 was, similar to the overall sample, statistically associated with a difference in clinical recognition for either gender whether considered as an ordinal or continuous variable. Again, BMI difference was not statistically significant for either gender when considered as a continuous variable. In this gender segregated analysis, however, the BMI group difference between round 1 and 2 was only significant for males with those with no change in BMI group most likely to be clinically recognized (32.0%) compared to those with increasing (18.2%) or decreasing (16.0%) BMI group.

Table 26

Bivariate Analysis of BMI Characteristics Comparing Those with Clinically Recognized and Unrecognized OSA Among Those at High BQ risk by Gender

BMI Variable	*p*-values [a]		
	All	Male	Female
Round 2[b]	<0.0001 [c]	<0.0001 [c]	<0.0001 [c]
Round 2 group	<0.0001	0.0037	0.0030
Round 1[b]	<0.0001 [c]	<0.0001 [c]	<0.0001 [c]
Round 1 group	<0.0001	0.0005	0.0056
Difference, round 2 – round 1[b]	0.47	0.23	0.92
Group difference, round 2 – round 1	0.012 [c]	0.041 [c]	0.33

[a] *p*-values represent chi square likelihood ratios for categorical variables and comparison of means by Student's t-test for continuous variables. [b] Continuous variable. [c] Parameter considered statistically significant and retained in the initial multivariate logistic regression model. Where continuous and ordinal variables are both significant only the continuous variable was retained.

OSA is associated with a number of chronic medical problems including cardiovascular disease (Caples et al., 2007), cerebrovascular disease (Yaggi et al., 2005), metabolic syndrome (Coughlin et al., 2004), and hypertension (Duran et al., 2001). It is conceivable that participants with these other medical problems would be more likely to have been clinically recognized with OSA with the care provided for these problems than those without such problems. PAVD study participants have been well characterized with regard to cardiovascular disease, myocardial function, and a variety of other medical co-morbidities. Thus, bivariate analyses of selected measures of cardiovascular disease and other co-morbidities were carried out.

Table 27

Bivariate Analysis of Clinical Characteristics Comparing Those with Clinically Recognized and Unrecognized OSA Among Those at High BQ Risk

Clinical Characteristic	BQ High Risk (n)	Mean [a]		Clinical Recognition (%)[b]		*p* [c]		
		Recog-nized	Unrecog-nized	With	Without	All	Male	Female
Atrial fibrillation or flutter	49			28.6	22.2	0.32	0.52	0.92
Coronary artery disease (CAD)	140			23.6	22.5	0.78	0.29	0.83
NonCAD CV disease	279			22.9	23.9	0.77	0.48	0.96
Any CV disease	299			22.4	24.3	0.57	0.19	0.90
Congestive heart failure	23			34.8	22.3	0.18	0.22	0.95
COPD	50			28.0	22.8	0.40	0.57	0.99
Cerebrovascular accident	30			20.0	23.3	0.68	0.98	0.51
Diabetes mellitus (Type 2)	103			34.0	21.2	0.007 [d]	0.03 [d]	0.38
Hypertension	459			23.3	21.5	0.59	0.96	0.15
Echocardiogram parameters, round 2								
Diastolic myocardial dysfunction	308			23.7	20.4	0.32	0.18	0.92
Systolic myocardial function (EF%)	503	64.7	65.7			0.23	0.55	0.35
Left atrial volume index (ml/m^2)	680	27.4	25.7			0.039 [d]	0.20	0.45
Lipid profile analysis, round 1								
Total cholesterol (mg/dl)	701	196.9	203.2			0.047 [d]	0.59	0.46
Triglyceride (mg/dl)	702	167.4	154.1			0.088	0.03 [d]	0.90
HDL (mg/dl)	701	38.2	43.7			<0.0001 [d]	0.01 [d]	0.09
Calculated LDL (mg/dl)	701	125.3	128.7			0.24	0.32	0.85
Biometric parameters, round 2								
Hip size (cm)	705	112.2	106.4			<0.0001 [d]	<0.0001 [d]	<0.0001 [d]
Neck size (cm)	704	41.3	38.2			<0.0001 [d]	<0.0001 [d]	<0.0001 [d]
Waist (cm)	705	107.0	96.4			<0.0001 [d]	<0.0001 [d]	<0.0001 [d]
Waist-Hip Ratio	705	0.955	0.905			<0.0001 [d]	0.0003 [d]	0.59

[a] The means for the characteristic for those with clinically recognized and unrecognized OSA for both genders. [b] The rate of clinical recognition with and without the identified clinical characteristics for both genders. [c] *p*-values represent chi square likelihood ratios for categorical variables and comparison of means and Student t-test for continuous variables. [d] Parameter considered statistically significant and retained in the initial multivariate logistic regression model.

Based on the analyses in Tables 25 – 27 the following variables are included in an initial multivariate logistic regression analyses for OSA clinical recognition: gender, age, years of education, BMI at rounds 1 and 2, BMI group difference from round 1 to 2, type 2 diabetes mellitus, left atrial volume index, total cholesterol, HDL, hip circumference, waist circumference, neck size, and waist to hip ratio. Table 28 depicts the subsets of variables entered into the initial modeling of gender-stratified logistic regression analyses. In a stepwise manner factors with *p* values greater than 0.05 were removed from the model until all remaining variables were statistically significant. The odds ratios from the resulting final model are depicted in Table 29.

Table 28

Factors Identified from Bivariate Analyses for Inclusion in the Initial Multivariate Logistic Regression Models for the Prediction of OSA Clinical Recognition

All	Male	Female
Gender		
Age (years)		
Education (years)	Education (years)	
BMI, round 1	BMI, round 1	BMI, round 1
BMI, round 2	BMI, round 2	BMI, round 2
BMI group difference	BMI group difference	
Diabetes mellitus, type 2	Diabetes mellitus, type 2	
LA volume index		
Total cholesterol		
	Triglycerides	
HDL cholesterol	HDL Cholesterol	
Hip circumference	Hip circumference	Hip circumference
Neck circumference	Neck Circumference	Neck Circumference
Waist circumference	Waist circumference	Waist circumference
Waist-Hip Ratio	Waist-Hip Ratio	

Table 29

Adjusted ORs for Clinical Recognition of OSA Among Those at High Risk by BQ with Gender Stratified Analysis

	OR	95% CI	*p*
All (n=686)			
Education, total (1 year)	1.10	1.03 – 1.19	0.005
BMI, round 1 (5 kg/m^2)	1.48	1.21 – 1.81	0.0001
Neck circumference (2.5 cm)	1.44	1.27 – 1.64	<0.0001
		R^2=0.1217	
Male (n=395)			
Education, total (1 year)	1.10	1.02 – 1.20	0.01
Waist (5 cm)	1.31	1.19 – 1.44	<0.0001
		R^2=0.0784	
Female (n=298)			
BMI, round 1 (5 kg/m^2)	2.02	1.52 – 2.75	<0.0001
		R^2=0.1021	

This modeling demonstrates that most of the variables in the mixed gender analysis apply to only one of the two gender-specific analyses. An additional mixed gender model was therefore constructed with interaction terms for each of these variables with gender; however, none of these interaction terms remained significant following stepwise regression. Given the significant differences between the genders a mixed gender analysis was performed with gender being retained throughout the stepwise regression even when not statistically significant. The model resulting from this analysis is depicted in Table 30.

Table 30

ORs for a Final Logistic Regression Model with Gender Included

	OR	95% CI	*p*
	All (n=686)		
Gender (male as reference)	0.76	0.55 – 1.03	0.08
Education, total (1 year)	1.10	1.02 – 1.18	0.009
BMI, round 1 (5 kg/m^2)	1.66	1.31 – 2.11	0.0001
Neck circumference (2.5 cm)	1.27	1.05 – 1.54	<0.0001
		R^2=0.1259	

This model suggests that education, BMI, and neck circumference are the primary predictors of clinical recognition with a 1 year educational increase increasing the likelihood of recognition by about 10%, a BMI increase of 5 kg/m^2 increases the likelihood of recognition by about 66%, and an 2.5 cm increase in neck circumference increases the likelihood of recognition by 27%. Though gender only approaches statistical significance, this model suggests that, holding education, BMI, and neck circumference constant, women are 24% less likely to be recognized than men.

Research Question One

What proportion of those at high risk for OSA based on the Berlin Questionnaire have been clinically evaluated for OSA?

This study sought to determine the proportion of those at high risk for OSA based on the BQ that had been clinically-evaluated for OSA. The gold standard for the clinical diagnosis of OSA is PSG. The analysis that follows is based both on that gold standard, and a review of narrative descriptions in the clinical record describing participants' clinical evaluation.

The REP search process had been designed using a broad group of sleep-related diagnosis and procedure codes in an effort to identify those for whom the diagnosis had

been considered and evaluation pursued. The REP search had identified 417 participants in round 2 that had a sleep-related diagnosis or procedure. In addition, there were 37 of the 50 participants selected at random to valid the REP search criteria and six additional participants from round 2 that were manually reviewed giving a total of 460 clinical records that were reviewed.

As demonstrated in Table 31 these reviews identified a total of 192 clinician reported diagnoses of OSA at the mild level or greater. In addition, there were five participants that had PSG and met AHI criteria for OSA but did not receive a clinician verified OSA diagnosis. These five participants had diagnoses reported as mild upper airway resistance syndrome, REM-related apnea, periodic leg movement disorder (2), and for one the PSG had been performed only as part of a study protocol. Because these participants PSGs met criteria for mild OSA with AHI's ranging from five to 17, these participants were considered to have clinically recognized OSA for the purpose of this analysis.

Of the remaining 263 records that were reviewed there were an additional 18 that had OSA-related diagnoses but were not formally diagnosed as having OSA including six that had undergone PSG. These diagnoses included upper airway resistance syndrome (UARS), snoring, and possible sleep disordered breathing (SDB) as well as possible OSA. Of the 12 of these participants that did not have PSG performed, the clinical record suggested that eight participants had declined further evaluation including PSG. The remaining 232 records included nonOSA related sleep diagnoses, most commonly insomnia or restless leg syndrome (RLS), which had prompted identification by the REP

search process. Therefore of the 460 records reviewed, there was evidence that at least 228 had been clinically evaluated more specifically for OSA including 204 for whom PSG had been performed. The validation of the REP search codes described above demonstrated that at least 95% of PAVD participants with OSA had been identified.

Table 31

Clinical Diagnosis and PSGs Performed for Round 2 Records Reviewed

Clinical diagnosis	n	PSGs
OSA, mild or greater	192	180
AHI-based criteria for OSA	5	5
OSA-related diagnosis	6 12[a]	6 0
NonOSA related diagnoses	13 232	13 0
Total	460	204

[a] For these 12 participants clinical records indicated that eight had declined PSG.

Of the 228 clinically evaluated 184 were classified as high risk by BQ, whereas 165 of the 204 undergoing PSG were at high risk. Thus, of the 705 participants at high risk for OSA based on the BQ, 26.1% (95% CI 22.9 – 29.3%) had undergone clinical evaluation for OSA including 23.4% (95% CI 20.3 – 26.5%) that had undergone PSG. Thus, the first null hypothesis for this study, "There is no difference between the population at high risk for OSA and those that have been clinically evaluated," is rejected

and the associated alternate hypothesis, "There is a portion of those at high risk for OSA that has not been clinically evaluated," is accepted.

Research Question Two

What is the prevalence of clinically diagnosed OSA among those at high risk for OSA based on responses to the Berlin Questionnaire?

The prevalence of clinically diagnosed OSA among those classified as high risk for OSA by the BQ, as described above in Table 23 and following is 22.7% (95% CI 20 – 26%). Recognizing that the BQ does not have a PPV or NPV of 100% the analysis in Table 23 demonstrated that the recognized prevalence could be as high as 23.6% (95% CI 21 – 26%). A demographic bivariate analysis (Table 24) demonstrated that this prevalence was substantially higher in males than females, 29.5% (95% CI 25 – 34%) vs 13.4% (95% CI 10 – 17%). In this analysis age also significantly predicts recognition with those recognized being, on average, 1.4 years younger (p=0.043) than those unrecognized.

Therefore the second null hypothesis for this study, "There is no difference between the population at high risk for OSA and those that have been clinically diagnosed," is rejected and the associated alternative hypothesis, "There is a portion of those at high risk for OSA that has not been clinically diagnosed," is accepted.

Research Question Three

Has the prevalence of clinically diagnosed OSA increased in the past decade?

Previous population-based studies of OSA clinical recognition, as shown in Table 32, reported clinical recognition rates in mixed gender populations from 8.3% and 15.4%

for moderate to severe OSA, and 6.5% for mild to severe OSA. The present study used the BQ for OSA identification. The best diagnostic performance of this instrument is for mild to severe OSA as shown in Table 6. Thus, the more comparable clinical recognition rates to those found in this study are those reported Young and colleagues (1997) based on criteria for mild to severe OSA.

Table 32

Previously Reported Prevalence of OSA Clinical Recognition for Those with OSA Stratified by Gender and Severity

Study	Gender	Prevalence of clinical recognition among those with OSA (95% CI)		Number with OSA (*n*)	
		moderate to severe	mild to severe	moderate to severe	mild to severe
Young, Evans et al., 1997	Male	18.2% (9.6 – 26.8%)	9.0% (4.5 – 13.5%)	77	93
Young, Evans et al., 1997	Female	7.4% (0 – 17.3%)	2.2% (0 – 5.1%)	27	155
Young, Evans et al., 1997	All	15.4% (8.5 – 22.3%)	6.5% (3.4 – 9.5%)	104	248
Kapur et al., 2002	All	8.3% (6.2 – 10.4%)	-	650	-

In Table 33 a comparison of these prevalence rates for both genders combined and gender specific samples, along with the applicable confidence intervals, with those found in this study demonstrates that the prevalence of clinical recognized OSA has significantly increased compared to rates reported in 1997. The clinically recognized prevalence in this study generally appears to be in the range of three to six times as high as that reported in the most comparable of the previous analyses (Young, Evans et al., 1997). However, there remains a large majority of OSA, 70.5 – 86.6%, depending on gender, which remains undiagnosed.

Table 33

Comparison of the Current Prevalence of OSA Clinical Recognition with Historically Reported Levels

	Prevalence of OSA clinical recognition (95% CI)		
	All	Male	Female
Young et al 1997	6.5% (3.4 – 9.5%)	9.0% (4.5 – 13.5%)	2.2% (0 – 5.1%)
Present study	22.7% (19.6 – 25.8%)	29.5% (25.1 - 33.9%)	13.4% (9.5 – 17.3%)
Prevalence Ratio	3.5 (2.1 – 5.8) [a]	3.3 (1.9 – 5.7) [a]	6.2 (1.5 - 25.8) [a]

[a] Confidence interval for rate ratio (Rosner, 2006, p. 757).

Therefore the third null hypothesis for this study, "There has been no change in the proportion of prevalent OSA that is diagnosed clinically compared to the mid-1990s," is rejected and the associated alternative hypothesis, "There has been an increase in the proportion of prevalent OSA that is diagnosed clinically compared to the mid-1990s," is accepted.

Research Question Four

What factors are predictive of the clinical diagnosis of OSA among those at high risk of OSA?

Bivariate analyses of OSA clinical recognition identified a number of factors associated with OSA clinical recognition in mixed gender and gender specific strata of this population as summarized in Table 28. Those factors include the demographic factors gender, age, and education, the biometric factors BMI, neck, hip, and waist circumference, and clinical factors related to diabetes and lipid profile. As noted above in Table 33 there was a statistically significant difference in the prevalence of OSA clinical recognition between the genders. In gender specific bivariate analysis, the factors associated with clinical recognition also differed between the genders.

Multivariate logistic regression analyses using these factors as described above in Table 29 identifies total years of education, BMI, and waist circumference as statistically significant predictors of OSA clinical recognition. Gender-specific logistic regression analysis demonstrates that years of education and waist size predict clinical recognition for men, whereas BMI is the lone predictor for women.

The unadjusted gender-specific prevalence rates for OSA clinical recognition in this population demonstrate that men are 2.20 times more likely to be recognized than women (29.5% vs 13.4%). However, analysis holding gender as a variable in a logistic regression model regardless of statistical significance suggests that there is only a 24% (p=0.08) lower clinical recognition rate when years of education, BMI, and neck circumference are held constant.

The null hypothesis related to this research question was "Among those at high risk for OSA there is no difference regarding the following characteristics among those with a clinical diagnosis of OSA than among those undiagnosed: age, gender, BMI, and socioeconomic status." In the null hypothesis four factors where hypothesized to be without difference between those diagnosed and undiagnosed: age, gender, BMI, and socioeconomic status. Among these factors age was identified as being different in bivariate, mixed gender analysis (Tables 24 and 28), but was not different in gender stratified bivariate analyses and not associated with clinical recognition when other factors were held constant in all of the multivariate analyses (Tables 29 and 30). Thus, for age, the null hypothesis is accepted.

Gender was also identified as being different in bivariate analysis (Tables 24 and 28). However, in multivariate analyses (Tables 29 and 30) gender nearly reached statistical significance with a confidence interval that just included unity (95% CI 0.55 – 1.03) and had a *p*-value of 0.08. However, because of the divergence of factors associated with clinical OSA recognition in gender stratified analyses (Tables 24, and 27 – 30) combined with this near statistical significance, the null hypothesis was de facto rejected for gender.

With respect to BMI, there was an association with a difference between those recognized and unrecognized with OSA in mixed gender and gender stratified bivariate analyses (Tables 25, 26, and 28). In multivariate analyses BMI was found to be statistically different in mixed gender analyses (Tables 29 and 30), but only for women in gender stratified multivariate analyses (Table 29). However, for men in gender stratified multivariate analysis another marker of obesity, waist circumference, was found to be associated with a clinical OSA recognition difference. Therefore, de facto for BMI recognized as a measure of obesity, the null hypothesis was also rejected.

Finally, with regard to socioeconomic status, this study represented socioeconomic status using education variables. Those variables included years of education, a continuous variable, and the dichotomous variable, "no more than high school" versus "at least some college." Only the continuous variable was found to be associated with a difference between those with recognized and unrecognized OSA in mixed gender analyses. In gender stratified bivariate analyses this variable was only associated with a difference for men. Similarly, in multivariate analyses, the variable was

only associated with a difference in mixed gender and male specific gender stratified analyses. Thus, for socioeconomic status, as represented by the variable years of education, the null hypothesis was rejected.

To summarize, the null hypothesis was accepted for age as follows, "Among those at high risk for OSA there is no difference regarding the following characteristics among those with a clinical diagnosis of OSA than among those undiagnosed: age." By contrast the null hypotheses were rejected, in some cases de facto, for gender, BMI, and socioeconomic status, and the following alternative hypothesis was accepted, "Among those at high risk for OSA the following characteristics will be more common among those with a clinical diagnosis of OSA than among those undiagnosed: male gender, higher BMI, and higher socioeconomic status [as represented by years of education]."

Summary

This study used data previously collected as part of the PAVD study (Redfield et al., 2003) which included responses to a modified BQ. Using the resources of the REP, those participants likely to have clinically recognized OSA were electronically identified and their clinical records systematically reviewed manually to obtain data regarding clinical PSGs performed and OSA diagnoses. To validate the REP identification process 50 randomly selected participants' records not identified by the REP process were also manually reviewed. Clinical records for an additional 20 participants not initially included in PAVD analyses but later identified as having completed the essential elements for the present study were also manually reviewed. Data from the PAVD

archive was then merged with data from the record review process to produce the single database for this study's analyses.

Analysis of this data first included validation of the REP electronic clinical OSA identification process. This validation demonstrated that the process was able to identify more than 95% of participants with clinical OSA with an estimated 98% of sleep-related diagnoses present at the time of the REP search detected by the process. The PAVD study was initiated with a population-based sample in 1997 (Ammar et al., 2006; Redfield et al., 2003). Participation bias had previously been assessed for those participating in round one of the PAVD study compared to the population-based sample (Jacobsen et al., 2004). A similar analysis of participation from round one to round two demonstrated underrepresentation of the youngest and oldest participants, women, those less educated, and those with co-morbidities generally based on the Charlson Index, and specifically related to COPD and nonCAD cardiovascular disease.

Descriptive analysis of OSA risk based on responses to the modified BQ demonstrated that nearly half (49.8%) of round two participants were at high risk of OSA. Based on comparison with the original BQ validation study (Netzer et al., 1999) it was estimated that the BQ modifications in this study could have underestimated OSA prevalence by no more than 15%. The REP guided chart review process identified a total of 197 round two participants with either a clinician reported or an AHI-based diagnosis of OSA. Of these 160 were among the 705 participants classified as high risk by the BQ giving a prevalence of OSA clinical recognition of 22.7% (95%CI 20 – 26%). Recognizing that this assumes the BQ to have 100% positive and negative predictive

values, the prevalence of OSA clinical recognition was recalculated using PPV and NPV values of 79% and 61%, respectively, for mild to severe OSA from the pooled analysis of BQ performance representing 586 participants in Table 6. The resulting prevalence of OSA clinical recognition, 23.6% (95% CI 21 – 26%), did not differ significantly from that based on the 100% PPV and NPV assumption. Thus, the remainder of the analysis used BQ high risk as an OSA proxy.

There was a substantial difference in unadjusted gender-specific prevalence rates for OSA clinical recognition in this population with men 2.20 times more likely to be recognized than women (29.5% vs 13.4%). Further bivariate analysis of OSA clinical recognition demonstrated that other demographic factors including age and education, biometric factors BMI, neck, hip, and waist circumference, and clinical factors related to diabetes and lipid profile all predicted OSA clinical recognition. However, multivariate logistic regression analyses identified total years of education, BMI, and waist circumference as the only statistically significant predictors of OSA clinical recognition in a mixed gender analysis. Gender-specific logistic regression analysis demonstrated that years of education and waist size predict clinical recognition for men, whereas BMI is the lone predictor for women. In mixed gender analysis, holding years of education, BMI, and neck circumference constant, there was only a 24% (p=0.08) lower clinical recognition rate for women compared to men.

Finally, though this analysis demonstrates that clinical recognition of OSA is three to six times greater compared to a previous population based analysis from the 1990s, OSA continues to be substantially (70.5 – 86.6%) under recognized clinically.

CHAPTER 5: SUMMARY, CONCLUSION, AND RECOMMENDATIONS

Overview

OSA is a disorder in which the airway collapses producing airway obstruction during sleep (Parish & Somers, 2004). It is associated with increased cardiovascular (Caples et al., 2007) and cerebrovascular (Yaggi et al., 2005) morbidity and mortality, and increased risk of metabolic syndrome (Coughlin et al., 2004), depression (Peppard et al., 2006), hypertension (Duran et al., 2001), and automobile accidents (Young, Blustein et al., 1997). Treatment of OSA, typically with CPAP, attenuates or reverses many of these associated risks (Doherty et al., 2005; Milleron et al., 2004; Peker et al., 2006). However, previous studies (Kapur et al., 2002; Young, Evans et al., 1997) based on 1990s data suggest that most OSA is clinically unrecognized.

This study sought to determine the proportion of those with OSA in the population who have been clinically evaluated and diagnosed. As a longitudinal benchmark, it also sought to determine if there had been a change compared to earlier published recognition rates (Kapur et al., 2002; Young, Evans et al., 1997). Finally, the study sought to identify factors predictive of clinical recognition. Once identified, these identified factors can then be used to propose strategies for enhanced clinical recognition that would represent a positive social change.

This study used data previously collected by the PAVD study to identify those at high risk for OSA based on a modified BQ. The resources of the REP were then used to identify participants with clinically recognized OSA. Based on a BQ-based OSA proxy, this study demonstrated that 22.7% (95% CI 20 – 26%) of those with OSA had been

clinically recognized including 29.5% (95% CI 25 – 34%) of men, but only 13.4% (95% CI 10 – 17%) of women. Though these rates of clinical recognition represent a three to six fold increase from those published more than a decade ago (Young, Evans et al., 1997), it is important to recognize that a majority of OSA remains clinically unrecognized despite this increased recognition. Multivariate logistic regression analysis identified education and measures of obesity including waist size for men, and BMI for women and mixed genders, and neck circumference in mixed gender populations, as predictors of clinical recognition.

Interpretation of Findings

The first three of the four stages in this study's analysis were designed to evaluate (a) the methods used to identify participants with clinically recognized OSA, (b) the potential for participation bias from round 1 to round 2 of the PAVD study, and (c) the performance of the high risk classification on the modified BQ as a proxy for OSA in the sample. Subsequently, in the fourth stage of the analysis, the research questions related to the prevalence of the clinical recognition of OSA are addressed.

Validation of REP Search Method to Ascertain OSA Clinical Recognition

A collection of sleep-related diagnostic and procedural codes had been used in search using the resources of the REP to electronically identify those likely to have clinical recognized OSA. The identified participants' clinical records were then systematically reviewed manually to obtain OSA-related data. A validation sample of 50 participants not selected in the electronic search was then manually reviewed to determine the validity of this electronic process in the identification of clinical recognized

OSA. The results of this 50 participant review are displayed in Table 13 and demonstrate that the electronic search had identified more than 95% of participants with clinical recognized OSA.

This validates the REP search process was being able to comprehensively identify essentially all participants in the sample with clinically recognized OSA. This method of ascertaining participants' status with regard to OSA clinical recognition is in contrast to those used in previously published studies (Kapur et al., 2002; Young, Evans et al., 1997) where participant self-report in a survey had been used to ascertain clinical OSA recognition. The earlier of these two studies had followed up with the 49 participants who had indicated that they had been told by a physician that they had sleep apnea (Young, Evans et al., 1997). In follow up, however, 33 of these participants admitted that they only suspected they had OSA and had not been clinically evaluated or diagnosed. No attempt was made in either of these studies to validate the responses of participants indicating that they did not have OSA. Thus, the method used here to ascertain OSA clinical recognition represents a substantial enhancement compared to previous methods.

Participation Bias from Round one to Round two of the PAVD Study

An earlier PAVD participation bias analysis (Jacobsen et al., 2004) had shown that, compared to the population-based sample invited, round one participants were more likely to have more than a high school education and less likely to have COPD. In addition, those from age 55 – 74 were more likely to have participated than those older or younger. Because the OSA clinical recognition outcomes in this study are based on the sample remaining in round two of PAVD, a similar participation bias analysis was carried

out comparing those participating in round two with those from round one who did not participate. That multivariate analysis, presented in Table 16, demonstrated that men were more likely to participate than women, whereas those with less education, COPD, cardiovascular disease other than coronary artery disease, and greater co-morbidities as measured by the Charlson Index (Charlson et al., 1987) were less likely to participate. With education limited to high school and the presence of COPD associated with lower levels of participation in both analyses, the round two under representation compared to the population-based sample for these variables is likely to be greater than that suggested by the Table 16 multivariate logistic regression.

With males over represented by about 24% (95% CI 2 – 53%) in round two, the overall prevalence of OSA in this sample is likely to be overestimated since men have been two to three times more likely to have OSA in the general population (Young, Peppard et al., 2002). Concurrently those with only a high school education are under represented by about 41% (95% CI 27 – 53%) which, based a previous study (Young, Evans et al., 1997), was associated with clinical under recognition of OSA. In a large epidemiologic study, OSA was found not to be associated with COPD (Sanders et al., 2003). Thus, the overall prevalence of OSA in the round two sample is likely unaffected substantially by the under representation of those with COPD. Both the Charlson Index and cardiovascular disease other than coronary artery disease (nonCAD CV disease) represent mixes of a variety of comorbidities making it difficult to meaningfully predict the impact of this under representation on the overall prevalence of OSA or its clinical recognition in the round two sample.

The participation bias analysis, based only on a consideration of factors for which prior associations with OSA prevalence or recognition exist, suggests that the round two sample appears more likely to overestimate the prevalence of OSA and its clinical recognition than to under estimate these parameters. The magnitude of these deviations from the original population-based sample invited to round one of the PAVD study, however, is not possible to predict. Using gender stratified analyses would limit the impact of the gender differential in round two participation.

Additional variables of particular relevance to this study's endpoints are those related to the performance of clinical PSG and the clinical diagnosis of OSA presented in Table 15. There was no statistical difference after adjustment for age and gender in the participation rates based on having undergone PSG, or having a clinical diagnosis of OSA. There also was no statistical difference in the rate of clinical evaluation by PSG ($p = 0.15$) or OSA diagnosis ($p = 0.15$) comparing those in round two with those not participating in round two prior to age and gender adjustment. Thus, though there may have been some over representation of those more likely to have OSA among round 2 participants, this appears not to have been significant enough to have led to increased clinical evaluation or clinical OSA recognition among round 2 participants. Because the potential over representation appears related to gender, the impact of this potential participation bias can be attenuated by the gender stratified analyses used in subsequent analyses.

Performance of the BQ High Risk Classification as the OSA Proxy

The BQ is an instrument designed to identify those likely to have sleep apnea (Netzer et al., 1999). As noted in Table 4 it has been used in some 30 previously published studies sometimes as a proxy for OSA. Table 5 identifies the 10 studies that have published PSG-based validation data for the instrument whereas Table 6 provides an analysis of its diagnostic performance at differing levels of OSA severity using data pooled from these validation studies.

The overall prevalence of OSA in this study based on the BQ OSA proxy was 49.8% (95% CI 47.2 – 52.4%) with gender specific prevalence of 57.9% (95% CI 54.3 – 61.5%) and 41.7% (95% CI 38.1 – 45.3%) for men and women, respectively, as illustrated in Table 19. This is substantially higher than all but one study (Redline et al., 2003) of the multiple studies reporting OSA prevalence summarized in Table 1. It is important to note, however, that the PAVD round two population is substantially older with a mean age of 65.2 (median 64.0) years and a range from 49.9 to 93.4 years compared to most studies in Table 1. Knowing that the prevalence of OSA increases with age (Young, Shahar et al., 2002), this higher prevalence may not be unreasonable for this older PAVD round 2 population.

The BQ was administered as part of the round 2 follow up evaluations in the PAVD study conducted from September of 2001 through March of 2005, after many of the studies in Table 1. With the increasing prevalence of obesity over time the prevalence of OSA in the population is also increasing (Young, Peppard, & Taheri, 2005). At round two 717 participants (50.6%) had gained weight since round one

whereas 166 (11.7%) had weights that were unchanged and 534 (37.7%) had lost weight. Thus the secular trend toward increased obesity prevalence generally, and as demonstrated for round two participants, would also predict a higher OSA prevalence compared to earlier studies.

This study's literature review described the variations in the questions included in the BQ from published applications of the instrument. The application in this study had excluded two questions from the original instrument due to concerns regarding vicarious liability (A.S. Gami, personal communication, July 17, 2007). As described in the analysis of the BQ results following Table 19, this variation would be expected to produce an underestimation of OSA prevalence by no more than about 15%. Thus, despite the BQ yielding an overall prevalence rate higher than most previous studies, the method used is likely still to have underestimated OSA prevalence.

The analysis of BQ diagnostic performance in this study presented in Table 21 demonstrates that, for those round two participants that underwent a clinical PSG, the sensitivity and positive predictive value of the BQ was over 80%. Consistent with the previously described test verification bias when a diagnostic instrument is applied in the clinical setting (Roger et al., 1997), the specificity and negative predictive value were much lower, in the range of 17 – 30%. Thus, the BQ in this study, similar to previous studies as illustrated in Table 5 and 6, was a substantially better instrument for predicting the presence of OSA than for predicting the absence of OSA.

Table 23 shows that the prevalence of clinical OSA recognition does not differ significantly when the PPV and NPV of the BQ are considered, compared to a prevalence

calculation that assumes a 100% PPV and NPV. This confirms that because this study considers the prevalence of clinical OSA recognition of those with OSA, the limited ability of the BQ to identify those without OSA has only a modest impact on the study.

In summary, the BQ as applied in this study appears to have been an effective tool in identifying OSA in the study population with the limitations of the instrument not significantly impacting the prevalence of OSA recognition. The higher prevalence rate for OSA compared to most previously reported studies may be related to the relatively older population studied, and a secular trend toward increasing obesity and OSA in the general population.

The Clinical Recognition of OSA

The central focus of this study is the four research questions regarding the clinical recognition of OSA. The results with regard to research questions one and two, as described in chapter 4 indicate that, of the 705 round two participants with BQ-based OSA, 26.1% (95% CI 22.9 – 29.3%) had undergone some type of clinical evaluation for OSA including 23.4% (95% CI 20.3 – 26.5%) that were evaluated with PSG. Of those with BQ-based OSA 22.7% (95% CI 20 – 26%) had clinically recognized OSA. Thus, only about one quarter of those with BQ-based OSA have been evaluated, and of those evaluated a large majority, 87.0%, were found clinically to have OSA. Of note, there were an additional 44 participants that did not have BQ-based OSA that had been clinically evaluated including 37 (84.1%) that were found to clinically have OSA.

These results suggest that nearly 75% of those with BQ-based OSA have not been clinically evaluated. Among those evaluated clinically, most are ultimately found to have

OSA regardless of whether they have BQ-based OSA. Thus, it appears that if the clinical care system pursues an OSA clinical evaluation regardless of their BQ-based risk, most (84.1 – 87.0%) were ultimately be shown to have OSA. However, a majority of those with OSA are never clinically evaluated or recognized. Therefore it appears that healthcare system continues to substantially under recognize OSA.

With regard to research question three, as presented in Table 33, a comparison of these prevalence rates for OSA clinical recognition with those previously published (Young, Evans et al., 1997) suggests that there has been a substantial improvement over time. The level of improvement was the most substantial among women with a prevalence ratio for clinical recognition of 6.2 (95% CI 1.5 – 25.8). Clinical recognition has increased by 3.3 (95% CI 1.9 – 5.7) times for men since the report of Young and colleagues in 1997. For a total, mixed gender population, recognition has increased 3.5 (95% CI 2.1 – 5.8) times. Thus, though the prevalence of OSA clinical recognition has improved substantially compared to rates published more than a decade ago (Young, Evans et al., 1997), the clinical care system still fails to recognize a substantial majority, about 75%, of OSA in the community.

Research reports have suggested that there had been increased health practitioner education regarding OSA during the decade of the 1990s (Haponik, 1992; Papp et al., 2002). Though there have been no more recent reports quantitatively documenting further curricular enhancement since 2002, a description of one institution's use of hand held digital devices to provide a podcast sleep curriculum to neurology residents has been

described (Gamaldo & Salas, 2008) suggesting that at a minimum some institutions have developed creative solutions to enhancing physician sleep training.

The increased rate of clinical recognition during a time when there was evidence of increasing sleep instruction for clinicians would be consistent with the theoretical basis for this research. That basis was the theory of hypothesis generation which requires the diagnostician have some prior knowledge of a disorder in order for that disorder to be included among the diagnostic hypotheses generated in evaluating a patient (Bockenholt & Weber, 1993; Round, 2001). Thus, these results would support an increased physician awareness of OSA leading to increased clinical recognition.

In addressing research question four regarding factors predictive of OSA clinical recognition, Tables 29 demonstrated that factors predicting recognition in the mixed gender model tend to segregate to only one gender in the gender stratified analyses. In these gender stratified models, increased education and waist size are predictive of recognition for men, whereas only BMI is predictive for women. In addition, when gender is retained regardless of statistical significance in a stepwise regression (Table 30), it remains nearly significant ($p = 0.08$) in the final model with men more likely to be recognized, whereas greater education, BMI, and neck circumference are statistically significant predictors of clinical recognition.

Based on this review of this study's results and the analysis of the null and alternative hypotheses the following conclusions were drawn:

1. There is a portion of those at high risk for OSA that has not been clinically evaluated.

2. There is a portion of those at high risk for OSA that has not been clinically diagnosed.
3. There has been an increase in the proportion of prevalent OSA that is diagnosed clinically compared to the mid-1990s.
4. Among those at high risk for OSA there is no difference regarding the following characteristics among those with a clinical diagnosis of OSA than among those undiagnosed: age.
5. Among those at high risk for OSA the following characteristics will be more common among those with a clinical diagnosis of OSA than among those undiagnosed: male gender, higher BMI, and higher socioeconomic status [as represented by years of education].

In summary, it would appear that OSA clinical recognition is generally best predicted by the classic OSA description of the Pickwickian Syndrome (Conti et al., 2006), that is, primarily those with obesity or male gender. The predictive marker for obesity varies by gender (Table 29) with waist circumference being the better multivariate predictor in male populations whereas BMI is more predictive for females. In the mixed gender model (Table 30) both neck circumference and BMI are statistically significant predictors. Finally, in predictive models for men and in mixed gender populations education is a statistically significant predictor of clinical OSA recognition.

Implications for Social Change

This study's results have implications for public health and for the clinical practice of medicine. The unadjusted odds ratio for gender as a predictor of OSA clinical

recognition is 0.37 (95% CI 0.25 – 0.55) suggesting substantially lower clinical recognition among women. In multivariate analysis, holding education, BMI, and neck circumference constant, the adjusted odds ratio is only 0.76 (95% CI 0.55 – 1.03) suggesting a much smaller differential by gender in OSA clinical recognition. It would seem that strategies targeted toward enhancing clinical recognition in women could be helpful in addressing this disparity.

The statistically significant disparities associated with the measures of obesity including BMI, and biometric parameters including hip, waist, and neck size, along with waist-hip ratio in mixed gender and gender stratified bivariate analyses. In multivariate analyses both for mixed gender and gender stratified populations a differing measure of obesity always remained significant in the adjusted models presented in Tables 29 and 30.

A review of the bivariate analysis of OSA clinical recognition stratified by BMI (Table 25) shows that none of the underweight participants with BQ-based OSA had been clinical recognized, whereas those in the normal and overweight classifications (BMI 20 – 29) had clinical recognition rates no more than about half of those with obesity (BMI ≥30).

A gender stratification of this bivariate analysis, as shown in Table 34, demonstrates that prevalence of OSA clinical recognition for the nonobese is less than for the obese in both genders, and that women are less likely recognized with OSA. The gender stratified relative risks of recognition for the nonobese compared to the obese are 0.56 (95% CI 0.40 – 0.77) and 0.31 (95% CI 0.15 – 0.64) for males and females,

respectively. These confidence intervals indicate that, in this sample, the differential in OSA recognition rates between nonobese and the obese is not statistically different between males and females. Thus, it seems quite clear that those with OSA who are not obese are significantly less likely to be clinically diagnosed, and women are much less likely to be recognized than men regardless of obesity.

Table 34

OSA Clinical Recognition Rates by Obesity (BMI ≥30) and Gender

	High risk by BQ, n			OSA clinically recognized, n (%)			
	All	Male	Female	All	Male	Female	p[a]
BMI <30	311	177	134	44 (14.2%)	36 (20.3%)	8 (6.0%)	0.0002
BMI ≥30	394	230	164	116 (29.4%)	84 (36.5%)	32 19.5%)	0.0002
Total	705	407	298	160 (22.7%)	120 (29.5%)	40 (13.4%)	<0.0001

[a] p-value for the Chi square likelihood ratio for the male - female comparison.

This reduced clinical recognition of OSA among the nonobese appears to confirm a hypothesis generated from a study of OSA in patient samples drawn from military and civilian populations where obesity was less prevalent in the military sample (Lettieri et al., 2005). That study noted that obesity was common among those with OSA, but recommended that BMI not be used as a criterion for identifying which patients should undergo evaluation for OSA.

Thus, developing strategies to educate clinicians regarding the overall low clinical recognition of sleep apnea, with substantially lower recognition rates for those with a BMI less than 30, and among women would be expected to lead to improved clinical recognition of OSA with associated increased likelihood of OSA treatment and prevention of the OSA associated morbidity and mortality. In addition, public education

efforts to raise the awareness of sleep apnea in general, and the fact that OSA affects both men and women, and though more common among the obese, is more commonly unrecognized among the nonobese would also encourage more people to seek evaluation for OSA. Together these strategies would lead to a positive social change with respect to the impact of sleep apnea on society.

Strengths of the Study

This study was conducted within a large, population-based longitudinal cohort study originally focused on ventricular dysfunction (Redfield et al., 2003). Since the components focusing on OSA were initiated in round two of that study, the study population was well characterized with regard to many cardiovascular and biometric variables both at the time of the BQ was administered, and four years previously. Thus, potential associations between these variables both at the time of BQ administration and four years previously with OSA clinical recognition were able to be explored.

The two previous studies of OSA clinical recognition (Kapur et al., 2002; Young, Evans et al., 1997) had used participant self-report to identify those with clinically recognized OSA. In verifying these reports from a survey by contacting the participants by telephone Young and colleagues (1997) found that only 33% had actually been clinically diagnosed whereas the remainder only personally suspected OSA. In addition, in this study there had been no effort to validate responses indicating the lack of a clinical OSA diagnosis. Kapur and colleagues (2002) did not attempt to validate self-reported clinical recognition in their study. Thus, this study is the first population-based study in which OSA clinical recognition has been validated by review of the clinical records.

In addition, this study used the resources of the REP to identify records documenting clinical recognition of OSA. The REP has been shown to retrieve records for 96% of the Olmstead County population (Melton, 1996). The codes used by the REP search in this study were validated and demonstrated that more than 95% of those with OSA in the study population were identified. Thus, the methods used in this study provide an essentially complete enumeration of all of the participants in this study population with clinically recognized OSA.

In summary, the primary strength of this study was the use of the resources of the REP to identify those with clinically recognized OSA and to validate the diagnosis using the original clinical records. As such, this is the first population based study of OSA clinical recognition to utilize such a rigorous method to validate clinical recognition. In addition, the study was carried out in a well characterized population both at the time of the BQ OSA determination, and longitudinally from four years previously.

Limitations of the Study

The assessment of OSA clinical recognition was conducted as part of the round two analyses in a larger longitudinal cohort study (Redfield et al., 2003). Thus, the sample studied represented those returning an average of four years following the initial round one assessment of the respondents to original population-based invitations to participate in the study. Those completing the BQ were only those that chose to participate in the study on two separate occasions four years apart. This method then has potential for participation bias.

Round one multivariate participation bias analysis (Jacobsen et al., 2004) had identified overrepresentation of those with more than a high school education, those between the ages of 55 – 74 years old, and those without COPD. As presented in Table 16, multivariate participation bias from round one to round two demonstrated the same age, education, and COPD biases that were identified in round one. In addition, female gender and the presence of nonCAD CV disease, along with a score of three or greater on the more general Charlson Index (Charlson et al., 1987) of comorbidities predicted under representation in round two. However, the clinical diagnosis of OSA and clinical testing by PSG was not associated with a differential in round two participation. With gender being among the factors associated with participation, the performance of gender specific analyses was one means of dealing with gender-based participation bias in this study.

The round two sample was 97.7% Caucasian, non-Hispanic which is an under-representation of other races and ethnicities. The US Census had shown that the Olmstead County population as a whole was only 95.3% and 89.0% Caucasian, non-Hispanic in 1990 and 2000, respectively (US Census Bureau, 2010). Thus, the results of this study cannot be extrapolated to non-Caucasian and Hispanic populations.

With a mean age of 65.2 years and the youngest participant being age 49.9 years old at the time the BQ was administered, this study's sample was older than both of the previous studies of OSA clinical recognition. The mean age in the study by Kapur and colleagues (2002) though younger was similar at 63.1 years. However, the study by Young and colleagues (1997) had an age range from 30 – 60 years and the mean ages of those with screen detected and clinically recognized OSA were all in the 40s, younger

than the youngest participant in the current study. Thus, comparison of the results in the present study with those of Young and colleagues (1997) must be done with caution. In addition, the ability to extrapolate these results to a younger adult population less than age 50 is also limited.

This study used the high risk classification on the BQ as an OSA proxy whereas the gold standard for OSA diagnosis is laboratory based PSG. Based on previously published validation analyses of the BQ and analysis of the clinical PSGs performed in the study population, the instrument has stronger diagnostic performance for OSA identification than for identifying those without OSA. In Table 23 a comparative analysis of OSA clinical recognition when the PPV and NPV of the BQ are considered, compared to a prevalence calculation that assumes a 100% PPV and NPV demonstrated no statistically significant difference. However, there may be some segments of the population in which there is an unrecognized differential in the diagnostic performance of the BQ. Thus, this study is limited by the lack of a gold standard OSA ascertainment method.

This study was carried out in Olmsted County, Minnesota where there are two sleep laboratories, one at Mayo Clinic with 24 beds and performing 4,440 PSGs annually (Mayo Foundation for Medical Education and Research, 2010), and a second smaller sleep lab at Olmsted Medical Center (Olmsted Medical Center, 2008). Therefore the participants in this study have comparatively easy access to sleep medicine services compared to many communities. Thus, the prevalence of clinical OSA recognition may

be higher in this community than other settings with comparatively limited access to sleep medicine services.

In summary, the limitations of this study include differential participation subsequent to the population-based sampling conducted in 1997 that appears to be related to age, gender, education, COPD, nonCAD CV disease, and general comorbidities as measured by the Charlson Index (Charlson et al., 1987). The impact of these biases appears to be limited as the evaluation rate with clinical PSG and the rate of OSA diagnosis did not differ between round two participants and nonparticipants. The impact of the gender-based biases on this study's results has been attenuated by use of gender stratified analyses. Because of the sample's demographics results should not be extrapolated to non-Caucasian and Hispanic population, or to populations younger than 50 years old. In addition, because the study used the BQ as a proxy for OSA rather than a laboratory-based PSG method, the diagnostic limitations of the BQ must be considered in interpreting the results. Finally, the study was conducted in a community with relatively easy access to sleep medicine services, thus the prevalence of OSA clinical recognition for this population may be higher compared to other communities with more limited access to these services.

Recommendations for Action

In 2006 the Institute of Medicine (IOM) concluded that "although clinical activities and scientific opportunities in the field [of sleep medicine] are expanding, awareness among the general public and health care professionals is low given the magnitude of the burden" (Colten & Altevogt, 2006, p. 1). The IOM recommended that

there be "increase[d] awareness of the burden of sleep loss and sleep disorders among the general public" (p. 3) and "expand[ed] awareness among health care professionals through education and training" (Colten & Altevogt, 2006, p. 3).

The present study suggests that, there may have been some improvement in OSA clinical recognition since the analysis by Young, Evans, and colleagues (1997). However, the majority, about 75%, of OSA in this older adult population remains unrecognized, with women, the nonobese, and those less well educated even more likely to be unrecognized. Thus, this study would support further expansion of both health professional and public education regarding OSA.

Given the population segments most under-recognized (i.e. women and the nonobese) these educational efforts should be carefully structured so as not to portray OSA as a disorder of obese men while still acknowledging that male gender and obesity are risk factors for OSA. In addition, noting that years of education was a predictor of OSA clinical recognition (Table 30) such public educational efforts should be structured in a manner making them meaningful regardless of educational level.

Where there are large clinical care systems that share a common electronic medical record system, it may also be possible to develop a set of electronic markers that predict OSA. For example, either using data from already existing tools by which patients report their symptoms, or by modifying such tools to include OSA-related symptoms, and adding other electronically recorded data such as BMI and the diagnosis of hypertension, it may be possible to construct an automated electronic BQ or similar algorithm predictive of OSA. This electronic BQ could then function in the background

and provide clinicians an electronic message that the patient is at high risk for OSA and suggest further testing.

Recommendations for Further Study

Because generalization of these results is limited by the lack of racial and ethnic diversity, and the relatively older population studied, repeating or expanding the study population to include younger adults and greater racial and ethnic diversity would be of value. The additional participants could then be selected using a population-based sampling method that could further attenuate the participation bias that resulted from this study's placement at round two of an ongoing study. With the existing round two cohort there would also be value in pursuing follow up to assess the impact of the BQ-based OSA classification on longitudinal outcomes.

With OSA ascertainment in this study having been based on the BQ whereas PSG represents the gold-standard for OSA diagnosis using PSG-based ascertainment in further study would be advantageous. Because of the cost of in laboratory PSG, use of in home unattended PSG may be an acceptable, cost-efficient alternative recognizing that at least one large population-based study had already used such a method (Quan et al., 1997). An additional alternative would be to study by PSG a randomly selected sample of the study population for validation of the BQ.

In parallel with the potential development of an automated electronic BQ for a larger clinical care system, research analysis of the impact of implementing such a system would be of significant value. Such research could then be used to validate the electronic algorithm, and ultimately document the impact of such a system on clinical outcomes

that, in the long-term could include cardiovascular disease, cerebrovascular accidents, hypertension, and diabetes.

Thus, this study's results provide a spring board to pursue OSA-related research addressing a variety of issues of both scientific and public health value.

Concluding Statement

Obstructive sleep apnea (OSA), a disorder in which the airway collapses causing an airway obstruction during sleep, is associated with multiple morbidities and increased mortality. Treatment of OSA, typically with continuous positive airway pressure (CPAP), attenuates or reverses many of these associated risks. Historically most OSA was clinically unrecognized and thus, untreated. Improved physician awareness of OSA and increased availability of sleep medicine services should predict increased recognition of OSA since it was last evaluated using data from the 1990s.

This study demonstrated an increase in clinical recognition from 6.5% (95% CI 3.4 – 9.5%) to 22.7% (95% CI 19.6 – 25.8%) overall in a mixed gender population. However, this still indicates that a majority of OSA, about 75%, remains unrecognized and thus, still untreated. Bivariate and multivariate analyses of OSA clinical recognition in this study demonstrated that, OSA recognition is most likely for obese men, that is, those that more closely resemble the classic Pickwickian Syndrome description. Conversely, women and the nonobese are among those less likely to be recognized with OSA.

Consistent with the IOM's 2006 statement titled, *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem* the results of this study point to the need

for increased clinician and public education about OSA, its diagnosis and treatment. Such educational efforts should highlight both the risk factors for OSA and risk factors that are currently associated with clinical under-recognition of the disorder. Concurrent development of systems-based tools built into electronic medical record systems that automatically alert clinicians to their patients' OSA risk would also have the potential to enhance OSA recognition and treatment, and lead to a reduction in OSA-related morbidity and mortality.

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Weaver, T. E., Maislin, G., Dinges, D. F., Bloxham, T., George, C. F., Greenberg, H., et al. (2007). Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep, 30*(6), 711-719.

Weinreich, G., Plein, K., Teschler, T., Resler, J., & Teschler, H. (2006). [Is the Berlin questionnaire an appropriate diagnostic tool for sleep medicine in pneumological rehabilitation?]. *Pneumologie, 60*(12), 737-742.

Weiss, N. S. (2008). Clinical Epidemiology. In K. J. Rothman, S. Greenland & T. L. Lash (Eds.), *Modern Epidemiology* (3rd ed., pp. 641-651). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

West, S. D., Nicoll, D. J., & Stradling, J. R. (2006). Prevalence of obstructive sleep apnoea in men with type 2 diabetes. *Thorax, 61*(11), 945-950.

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Wright, J., & Sheldon, T. (2000). The efficacy of nasal continuous positive airway pressure in the treatment of obstructive sleep apnea syndrome is not proven. *Am J Respir Crit Care Med, 161*(6), 1776-1778.

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Youden, W. J. (1950). Index for rating diagnostic tests. *Cancer, 3*(1), 32-35.

Young, T., Blustein, J., Finn, L., & Palta, M. (1997). Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. *Sleep, 20*(8), 608-613.

Young, T., Evans, L., Finn, L., & Palta, M. (1997). Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep, 20*(9), 705-706.

Young, T., Hutton, R., Finn, L., Badr, S., & Palta, M. (1996). The gender bias in sleep apnea diagnosis. Are women missed because they have different symptoms? *Arch Intern Med, 156*(21), 2445-2451.

Young, T., Palta, M., Dempsey, J., Skatrud, J., Weber, S., & Badr, S. (1993). The occurrence of sleep-disordered breathing among middle-aged adults. *N.Engl.J.Med., 328*(17), 1230-1235.

Young, T., Peppard, P., Palta, M., Hla, K. M., Finn, L., Morgan, B., et al. (1997). Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Arch Intern Med, 157*(15), 1746-1752.

Young, T., Peppard, P. E., & Gottlieb, D. J. (2002). Epidemiology of obstructive sleep apnea: a population health perspective. *Am.J.Respir.Crit Care Med., 165*(9), 1217-1239.

Young, T., Peppard, P. E., & Taheri, S. (2005). Excess weight and sleep-disordered breathing. *J Appl Physiol, 99*(4), 1592-1599.

Young, T., Shahar, E., Nieto, F. J., Redline, S., Newman, A. B., Gottlieb, D. J., et al. (2002). Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. *Arch Intern Med, 162*(8), 893-900.

Zozula, R., Rosen, R. C., Jahn, E. G., & Engel, S. H. (2005). Recognition of sleep disorders in a community-based setting following an educational intervention. *Sleep Med, 6*(1), 55-61.

CURRICULUM VITAE

Mark Richard Zellmer

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EMAIL:	Home:	zellmer@centurytel.net	Office:	zellmer.mark@mayo.edu
PHONE:	Home:	(608)788-6468	Office:	(507) 255-9305
	Cell:	(608) 386-8647	Pager:	(507) 538-9642

EXPERIENCE:

May 2005 – present *Physician Assistant, Cardiology Hospitalist, Division of Cardiovascular Disease, Mayo Clinic, Rochester, MN:* Providing medical care to patients hospitalized on one of three cardiology services at St. Mary's Hospital. Initial evaluation, ongoing management, and the discharge of inpatients; supervised by a consulting cardiologist as part of a team of mid-level providers.

Sept. 1995 - present *Physician Assistant Clinical Practice, Gundersen Lutheran, La Crosse, WI:* Providing medical care for patients in the emergency room, hospital, clinic and nursing home at a rural regional practice site. Gundersen Lutheran-Hillsboro & St. Joseph's Memorial Hospital, Hillsboro, WI, September 1995-May 1996, Gundersen Lutheran-Whitehall & Tri-County Memorial Hospital, Whitehall, WI, June 1996 - present.

March 1995 – April 2005 *Associate Professor, Department of Health Professions, Director of the UW-L - Gundersen - Mayo Physician Assistant Program; Past Chair of Clinical Science, 1995-2002, University of Wisconsin - La Crosse, College of Science and Allied Health, La Crosse, WI:* Developing and implementing a physician assistant program representing a partnership of the Mayo School of Health Sciences in Rochester, Minnesota, and the Gundersen Lutheran Medical Foundation in La Crosse. Responsible for developing program curriculum and policies, accreditation materials, recruiting faculty and students, developing clinical sites, and building and maintaining institutional relationships for the program. Brought program to full accreditation in 1997, reaccredidation in 2000, and reaccredidation for six years in 2003. 100% of program graduates passed the NCCPA PANCE exam. Mean scores for seven classes have placed the program above the 87%ile, on average, among PA programs nationally. Primary instructor for courses on the History of the PA Profession (1995-2005) and Medical Epidemiology (1999-2005); Co-instructor for physical exam course and clinical problem-based curriculum. As Clinical Science Department Chair responsibilities had included establishing and managing the Clinical Science Department consisting of programs in Nuclear Medical Technology, Medical Laboratory Science, Occupational Therapy, and Radiation Therapy in addition to the PA Program. Member Faculty Senate 2000-2003. Member Joint Budget and Planning Committee, 2001-4.

Feb. 1993 - March 1995 *Associate Professor and Director of Physician Assistant Studies, University of South Dakota, School of Medicine, Division of Health Sciences, Vermillion, SD:* Developed the curriculum, admissions and other administrative policies for an new accredited PA program. Secured a federal grant for physician assistant training. Negotiated a private contract to expand the program by four students and one additional faculty member. Responsible for faculty and student recruitment, clinical training site development and building relationships for the

PA program with South Dakota institutions, agencies and other USD departments. Instructor for History and Physical exam course, Pathophysiology, and Didactic Clinical Medicine courses.

Oct. 1987 - March 1993 *Physician Assistant, Interstate Medical Center, Department of Internal Medicine, Red Wing MN, and Zumbrota, MN Satellite Clinic:* Providing medical care to patients in the clinic, nursing home, and hospital settings. Special clinical interests include geriatric care, rural and emergency medicine. Served on the Medical Center and nursing home Quality Assurance Review Committees and a nursing home Ethics Committee.

June 1983 - Sept. 1987 *Physician Assistant, Park Clinic-Allison, IA Satellite Office:* Providing a broad spectrum of primary care medical services to the residents of Allison, Iowa, a small, rural community with the supervision of physicians from a larger multispecialty clinic in Mason City, IA. Responsibilities included comprehensive primary care, 24 hour emergency call, EMT education, office and personnel management, and community relations.

EDUCATION:

2003 – 2010	PhD in Public Health, Epidemiology Emphasis Cumulative GPA 3.947, Dissertation completion anticipated 2010. Dissertation title: "Clinical Recognition of Obstructive Sleep Apnea in a Population-Based Sample" Walden University, Minneapolis, MN
2006, Fall	Graduate Course in Statistics, HSR5535: Introductory Statistical Methods II (Multivariate Analysis), Mayo Graduate School, Rochester, MN
2004, Summer	Graduate Summer Session in Epidemiology. Courses included: Design, conduct and analysis of clinical trials, Pharmacoepidemiology, and Systematic review/Meta-analysis University of Michigan, School of Public Health, Ann Arbor, MI
2001, Spring	Graduate special student: STAT 601 Statistics in Health Care Research Winona State University, Winona, MN
1981-1983	Bachelor of Science in Medicine, Physician Assistant Program, College of Medicine, University of Iowa, Iowa City, IA
1976-1977	Master of Arts, Science Education College of St. Thomas, St. Paul, MN
1972-1976	Bachelor of Arts, Chemistry and Natural Science Augsburg College, Minneapolis, MN
1972	High School Graduate, North High School, West Union, IA

CERTIFICATION:

Physician Assistant-Certified (PA-C), Primary Care. Scored in the top 5% on the Physician Assistant National Certification Exam, National Commission of Certification of Physician Assistants (NCCPA) in 1983. Recertified by examination 1990, 1996 2002, and 2008, scoring historically in the top 5% and most recently the top 3% in 2008.

LICENSURE:

Wisconsin Medical Examining Board, Physician Assistant, Number 507-023, expires February 29, 2012.
Minnesota Board of Medical Practice, Physician Assistant, Number 8874, expires June 30, 2011.

PEER REVIEWED PUBLICATIONS:

Zellmer, MR, Hadley, RD, A Descriptive Analysis of Capstone Project Requirements in Academic and Professional Physician Assistant Master's Degree Programs, *Perspective on Physician Assistant Education,* 2004; 15(2):82-87.

Carter, RD, Cawley, JF, Fowkes, V, Hooker, RS, Rackover, MA, Zellmer, MR, Blue Ribbon Panel Report on Physician Assistant Program Expansion, *Perspective of Physician Assistant Education*, Winter 1998; 9:(1)20-29.

Zellmer, MR and Valentine, P., The Education of PAs for Underserved Areas, *Proceedings of the National Health Service Corps 20th Anniversary Celebration: A Forum on Primary Care*, April 1993.

Zellmer, MR, The Ethics of Head Hunting, *Physician Assistant Newsletter of Ethics* (P.A.N.E.), Spring 1993; 3(3):4.

Zellmer, MR, A Survey of Minnesota Physicians Regarding Delegation of Prescriptive Practice to PAs, *Journal of the American Academy of Physician Assistants*, September 1992; 5:582-6.

GRANT AWARDS:

Author, Rural Interdisciplinary Healthcare Provider Course, Southwest Wisconsin AHEC, $1760 funded, June 2001.

Co-author of the grant proposal funded by the UW-L General Education Committee to support the development of cases for the course SAH 105: Analysis of Health, Wellness and Disease for the Health Care Consumer, $6000 approved, March 2000.

Author, "Analysis of Predictors of PA Program Student and Graduate Performance," University of Wisconsin - La Crosse, College of Science and Allied Health, Faculty development grant, 1999-2000, $1400.

Principle Investigator, "Investigation of Recruitment and Retention Issue for Physician Assistant in Rural Practice: A Pilot Study," Southwest Area Health Education Center, Inc, 1996, $3000.

Principle Investigator, PA Training Grant to the University of South Dakota, Division of Health Sciences, Title VII, Division of Medicine, Bureau of Health Professions, DHHS, 1994-1997, 1 D21 PE10075-01, $444,060.

BOOK CHAPTER:

Sert Kuniyoshi, FH, Zellmer, MR, Adachi, T, Somers, VK, (2010) Acute and Emergent Cardiac Events in Obstructive Sleep Apnea. In S. Chokroverty & P. Sahota (Eds), *Acute and Emergent Events in Sleep Disorders.* (pp. 15-32), New York: Oxford (in press).

PRESENTATIONS:

"Berlin Questionnaire Diagnostic Performance in published validation studies", Poster co-authored with C.S.P. Lam, MD, A.S. Gami, MD, E.J. Olson, MD, S.M. Caples, DO, and V.K. Somers, MD, PhD for SLEEP 2009, Seattle, WA, June 6-11, 2009.

"Obstructive Sleep Apnea, the Berlin Questionnaire, and the Prevalence of Clinical Recognition", Conference presentation for the research fellows in the Virend Somers, MD, PhD, laboratory group, Mayo Clinic, Rochester, MN, November 18, 2008.

"Research Involvement at Mayo Clinic", Panel presentation at the semi-annual NP/PA Forum, Mayo Clinic, Rochester, MN, November 10, 2008.

"Obstructive Sleep Apnea: A Critical Review of Population Prevalence", Poster Presentation, Internal Medicine Review for NPs, PAs and Primary Care Physicians, Mayo Clinic, Rochester, MN, September 17-19, 2008.

"A Snoring Lunch for the Heart: Obstructive Sleep Apnea & Related Disorders," Lunch and Learn presentation, Inpatient NP/PA Group, Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, May 6, 2008.

"Obstructive Sleep Apnea Risk in a Population-based Sample", Poster Presentation, Summer Residency, Walden University, Minneapolis, MN, July 18, 2007.

"Healthcare for Evacuees from Hurricanes Katrina and Rita: Operation Minnesota Lifeline", poster presentation, AAPA National Conference, San Francisco, CA, May 27-31, 2006.

PRESENTATIONS (continued)

"A Descriptive Analysis of Capstone Project Requirements in Academic and Professional Physician Assistant Master's Degree Programs," coauthor with Hadley, RD, poster presentation, Internal Medicine Review for Nurse Practitioners and Physician Assistants: A Case Study Approach to the Management of Common Problems, Mayo Clinic, Rochester, MN, September 15-16, 2005.

"A Descriptive Analysis of Capstone Project Requirements in Academic and Professional Master's Degree Programs," coauthor with Hadley, RD, paper presentation, Association of PA Programs Educational Forum, Phoenix, AZ, October 24, 2003.

"What constitutes a Master's Project?" co-presenter with Robert Hadley, PhD, PA-C, roundtable presentation, Association of Physician Assistant Programs, Semiannual Meeting, New Orleans, LA, May 23, 2003.

"PA Adjunct Faculty Development and Utilization: Models of Inclusion," co-presenter with Mare Wheeler, MS, PA-C, roundtable presentation, Association of PA Programs Educational Forum, Miami, FL, November 7, 2002.

"Update on the Male Genitourinary Exam," invited presentation, Minnesota Academy of PAs, Fall Conference, Rochester, MN, 28 September 2001.

"Don't Judge a Book by its Cover: An Overview of Medical Literature Interpretation," invited presentation, Wisconsin Academy of PAs, Fall Conference, Eau Claire, WI, October 21, 2000.

"Using the Medical Literature in Clinical Practice", invited presentation, American Academy of PAs Annual Conference, Chicago, IL, May 2000.

"A Review Process for Applying Research Literature to Clinical Practice", invited presentation, American Academy of PAs, Annual Conference, Chicago, IL, May 2000.

"Net Essentials for PAs", invited presentation, American Academy of PAs, Annual Conference, Chicago, IL, May 2000.

"Using the Medical Literature in Clinical Practice", Minnesota Academy of PAs, Fall CME Conference, September 1997, presenter.

"The Physician Assistant in Primary Care," in "Perspectives in Primary Care, A Symposium in Celebration of National Primary Care Day", sponsored by the SW Wisconsin AHEC, La Crosse, WI, September 28, 1995, panelist.

"Physician Assistant Education in La Crosse," Gundersen Medical Foundation Noon Conference, La Crosse, WI, September 25, 1995, presenter.

"Effective Use of NPs, PAs and CNMs" at the 1995 National Health Service Corps' "Recruitment in the 1990's: Challenges & Opportunities," May 25, 1995, St. Paul, MN, Co-presenter.

"An Update on PA Education In Minnesota," MAPA Spring CME, St. Louis Park, MN, April 7, 1995.

"Physician Assistants and PA Education in South Dakota," 9th Annual South Dakota Rural Health Conference, Pierre, SD, November 4, 1993, Presenter.

"The Clintons' Healthcare Reform Proposal in the view of the American Academy of Physician Assistants," the Rural Health Policy Board of the National Rural Health Association, November 12, 1993, Chicago, IL, Presenter.

"The Education of PAs for Underserved Areas", National Health Service Corps 20th Anniversary Celebration: A Forum on Primary Care, Arlington, VA, June 24, 1992, Co-Presenter.

"Panel Discussion: Physician Assistants in the Emergency Department", Advances in Emergency Medicine sponsored by the Minnesota Chapter of the American College of Emergency Physicians, Minneapolis, MN, May 1, 1992, Panelist.

"Rural Health/Inner City Initiatives: Can We Fulfill Our Original Professional Mandate?", North Central Regional Meeting of the AAPA, Lansing, MI, February 2, 1992, Presenter.

"Panel Discussion: PA Prescribing and Regulation in Minnesota", Minnesota Academy of PA Fall CME, Duluth, MN, October 27, 1991, Moderator.

"Membership Development Workshop: 24 Great Membership Ideas", AAPA Constituent Chapter Officers Workshop, Alexandria, VA, September 13, 1991, Panelist.

"Panel Discussion: What's New With Recertification, Information and Discussion", North Central Meeting of the AAPA, Minneapolis, MN, February 3, 1991, Moderator.

PRESENTATIONS (continued)

"Panel Discussion: PA Regulation, Which Model is Best, A Comparison of Several States' PA Regulatory Systems", North Central Meeting of the AAPA, Minneapolis, MN, February 2, 1991, Moderator.

"Practice Demographics and PA Salaries in Two North Central States: Implications for the Profession", North Central Meeting of the AAPA, Minneapolis, MN, February 2, 1991, Presenter.

ACCREDITATION SITE VISITOR:

Site visitor for the Accreditation Review Commission for Physician Assistant Education (ARC-PA)

Daemen College, Buffalo, NY, April 2006, team chair
Samuel Merritt College, Oakland, CA, June 2005
Grand Valley State University, Grand Rapids, MI, May 2004, team chair
Medical College of Ohio, Toledo, OH, January 2004, team chair
College of Health Sciences, Roanoke, VA, January 2003, team chair
University of Texas Health Science Center, San Antonio, Texas, July 2002, team chair
Central Michigan University, Mount Pleasant, MI, January 2002, team chair
Arcadia University, Philadelphia, PA, July 2001
Medical College of Ohio, Toledo, OH, January 2001
St. Francis University, Fort Wayne, IN, January 2000, team chair
St. Francis College, Loretto, PA, January 1999
New York Institute of Technology, Long Island, NY, July 1998
SUNY Downstate, Brooklyn, NY, January 1998, team chair
Grand Valley State University, Grand Rapids, MI, July 1997
Brooklyn Hospital/Long Island University, Brooklyn, NY, January 1997

OTHER MEDICAL EDUCATION:

2008-present	Advanced Trauma Life Support (ATLS), completion of provider course, St. Cloud, MN.
2007-present	Pediatric Advanced Life Support (PALS), Minnesota Affiliate, American Heart Association.
1983-present	Advanced Cardiac Life Support (ACLS), Provider 1983-present; Instructor 1983-2007. Iowa, Minnesota, Dakota and Wisconsin Affiliates of the American Heart Association
1983	Advanced Trauma Management Emergency Medical Services Learning Resource Center University of Iowa Hospital and Clinic, Iowa City, IA
1981	Instructor/Coordinator EMT Course, Mount Vernon Extension Class Kirkwood Community College, Cedar Rapids, IA
1981	Research Assistant for John Weiler, MD, Department of Allergy Immunology, University of Iowa. Performed Complement tissue culture research.
1980	EMT-Paramedic Emergency Medical Services Learning Resource Center University of Iowa Hospital and Clinic, Iowa City, IA
1979-80	EMT, Training Officer and Charter Member, Dumont Ambulance Service, Dumont, IA
1979	EMT-Ambulance, North Iowa Area Community College, Mason City, IA

OTHER MEDICAL EXPERIENCE:

June 1982- May 1983 Physician Assistant Program Clinical Rotations, University of Iowa PA Program, Iowa City, IA

Emergency Medicine	Schoitz Hospital, Waterloo, IA
Family Practice	Broadlawns Hospital, Des Moines, IA
	Muscatine Health Center, Muscatine, IA
	Franklin Medical Center, Hampton, IA
General Surgery	VA Medical Center, Iowa City, IA
Internal Medicine	Park Clinic, Mason City, IA
Obstetrics & Gynecology	University of Iowa Hospitals, Iowa City
Orthopedic Surgery	Muscatine General Hosp., Muscatine, IA
Pediatrics	Marshfield Clinic, Marshfield, WI
Psychiatry	VA Medical Center, Des Moines, IA

Sept. 1980 - March 1983 EMT-Paramedic, Mercy Hospital/Area Ambulance, Cedar Rapids, IA:
A hospital emergency room based ambulance service providing assessment, advanced cardiac life support and transportation to the sick and injured with ground and helicopter air ambulances.

OTHER WORK EXPERIENCE:

School Years 1978-1980 Senior High Science Instructor, Dumont Community School, Dumont, IA.
Taught Chemistry, Biology, and Physical Science. Coached Football, Basketball and Track.

Summer 1978 House Parent, Frontier Farm Group Home for Boys, Effie, MN
Parented boys ages 12-18 in the development of positive relations with peers, family and authority figures on a homestead farm.

School year 1977-78 High School Science Instructor, Villard Public School, Villard, MN: Taught Chemistry, Physics, Biology, and Life Science.

School year 1976-77 Science teaching intern, Bloomington Lincoln High School, Bloomington, MN.

Summer 1976 Nursing Assistant, Augustana Home for the Aged, Minneapolis, MN.

Summer 1975 Guide/counselor, Wilderness Canoe Base, Grand Marais, MN.

Summer 1974 Youth Service Corps Counselor, Woodward Hosp./School for the Retarded, Woodward, IA

Summers 1971-73 Camp Counselor, EWALU Bible Camp, Strawberry Point, IA.

GOVERNMENTAL APPOINTMENT:

Member, Rural Health Advisory Committee, Minnesota Department of Health, Office of Rural Health, 1992-1993.

PROFESSIONAL ORGANIZATION MEMBERSHIPS AND OFFICES:

American Academy of Sleep Medicine (AASM), Student member, 2005 to the present.

American Public Health Association (APHA), Student member, 2005 to 2009.

American Academy of Physician Assistants (AAPA), Fellow Member; Member since 1983; Official Liaison for the AAPA to the National Rural Health Association 1992-98; Chapter and Member Relations Committee, North Central Region Representative, 1992 - 1994; Member, Advisory Committee of PA Employment 1991-92; House of Delegates, Reference Committee Member 1993 & Observer 1992, Delegate 1989, 1992-93, Alternate Delegate 1990 & 1991; Coordinator for the North Central Regional meeting, February 1991; Reviewer, Taskforce on PA Specialty Practice report, 1993; Reviewer National Health Program Position Paper, 1990 & 1996; Reviewer of Rural Health Policy Paper, 1989.

Association of PAs in Cardiology, Member 2006-present.

PROFESSIONAL ORGANIZATION MEMBERSHIPS AND OFFICES (continued):

Rural Health Caucus of the AAPA, Member, 1991-1996; Newsletter Editor/Board Member At Large, 1992-1996; Charter member and Secretary-Treasurer, 1991-92.

South Dakota Academy of Physician Assistants (SDAPA), Fellow Member 1993-95, Legislative Committee, 1993-95.

Minnesota Academy of Physician Assistants (MAPA), Fellow Member since 1988; President 1991; Member Board of Directors 1988-1992; Board Liaison for development of a Minnesota PA Training Program, 1989-1993; Past Chair Legislative Committee, 1989-91; Past chair, Membership Committee, 1989-90; Member, ad hoc judicial affairs committee, 1992.

Association of Physician Assistant Programs (APAP), Director of member program, 1995-2005; Member, CASPA Steering Committee, 2004-present; Associate Member, 1990-1995; Member Leadership Training Institute Advisory Committee, 1994-1997; Reviewer, J. Peter Nyquist Writing Contest, 2003.

National Rural Health Association, Member, 1992-2004; Member Rural Health Policy Board, 1996-1998, Clinical Services Constituency Group.

American Geriatrics Society, Member, 1991-1995.

University of Iowa Student PA Society, Past Member and Past President, 1981-83.

AWARDS/HONORS:

Who's Who in Medicine and Healthcare, 1996, 2000, 2002

Who's Who in America, 1997

Minnesota Academy of Physician Assistants, Presidential Award, 1990 & 1993.

Who's Who Among American and College & University Students, 1975-76

Academic Achievement Award, Science Award, North High School, 1972

National Honor Society, North High School, 1971-72

COMMUNITY SERVICE ACTIVITIES:

Our Savior's Lutheran Church: Call Committee Chair, 2005, Church Council President, 2002, Board of Worship and Music, Chair, 1999-2001, Member 1999-present; Church council member, 1999-2003; Senior Choir Member, 1995-present; Sunday School Teacher, 1997-98, Our Savior's Lutheran Church, La Crosse, WI

Lutheran Campus Ministry, Chair, 1998-2003; Directing Committee Member, 1996-2003, Building Committee member, 2002-2004; La Crosse, WI

Soccer Coach, 1994, Vermillion Youth Soccer League, Vermillion, SD

Sunday School Teacher, 1993-94, Trinity Lutheran Church, Vermillion, SD

EMT Guest Instructor, 1993-94, Vermillion-Clay County Ambulance Service, Vermillion, SD

Sunday School Teacher, 1992-93 & 1989-91, Senior Choir Member, 1987-1993, United Lutheran Church, Red Wing, MN

Host Parent, American Field Service (AFS), foreign exchange program, 1989-90, Red Wing, MN

Member, Dawnbreaker Kiwanis Club, 1987-1992, Red Wing, MN

Member Red Wing American Field Service Chapter, 1989-1992, Red Wing, MN

Past President, Butler County Chapter, American Heart Association, Allison, IA

Member and President, Allison Lions Club, Allison, IA, 1984-87

Member, Medi-Search, Ltd., 1979-80, a community physician recruitment committee, Hampton, IA

Host Parent, 1979-80, Youth For Understanding, Dumont, IA