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Incidence of Hypertension and Type 2 Diabetes Among Obstructive Sleep Apnea Patients

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ABSTRACT

Incidence of Hypertension and Type 2 Diabetes among Obstructive Sleep Apnea Patients

By

Dedria Nicole McArthur

May 3, 2016

Background: Obstructive Sleep Apnea (OSA) is a chronic breathing disorder that is estimated to affect 20% of the US adult population. Intermittent hypoxia and sleep fragmentation caused by OSA likely affects cardiometabolic function. Individuals with OSA might be at risk of developing hypertension and type 2 diabetes (T2DM), with a dose-response relationship related to OSA severity. The objective of this study was to estimate the association between severity of OSA at diagnosis with 1) incidence of hypertension incidence of hypertension and 2) incidence of T2DM.

Methods: We conducted a retrospective cohort study of Kaiser Permanente members diagnosed with OSA during 2000-2005. Adults without baseline hypertension or T2DM were eligible. Patients were excluded if hypertension or T2DM was diagnosed within one year prior to OSA diagnosis, and right censored at the end of follow-up or at the time Kaiser Permanente membership ended. Kaplan-Meier curves and Cox Proportional Hazard models were used to estimate the association between OSA severity and incident hypertension and incident diabetes.

Results: Overall 719 patients were diagnosed with OSA during the study periods; 614 were included as those at risk of developing either hypertension (N=265) or T2DM (N=489). Overall, 261 had severe OSA at diagnosis. Those with severe OSA were more likely to be middle aged, overweight, and have prevalent hypertension or T2DM. Among those without prevalent hypertension at OSA diagnosis, 47.4% (126/266) were subsequently diagnosed with hypertension. Among those without prevalent T2DM at OSA diagnosis, 16.3% (80/491) were subsequently diagnosed with T2DM. After adjusting for BMI and prevalent T2DM, the hazard rate of incident hypertension among patients with severe OSA was 1.35 (95%CI: 0.88-2.06) compared to the rate among patients with mild OSA. The hazard rate of incident T2DM among patients with severe OSA was 1.49 (95%CI: 0.83-2.67) compared to the rate among patients with mild OSA after adjusting for BMI and prevalent hypertension.

Discussion: We found high incidence rates of hypertension and T2DM among adults diagnosed with OSA. Severe OSA at diagnosis was associated with increased risk of either incident hypertension or T2DM, but not significantly (for $p \leq 0.05$).

Incidence of Hypertension and Type 2 Diabetes among Obstructive Sleep Apnea Patients

by

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B.S., Auburn University

A Thesis Submitted to the Graduate Faculty
of Georgia State University in Partial Fulfillment
of the
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APPROVAL PAGE

Incidence of Hypertension and Type 2 Diabetes among Obstructive Sleep Apnea Patients

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Author's Statement Page

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Chapter 1: Introduction

1.1 Background

Obstructive sleep apnea (OSA) is a chronic condition that is characterized by frequent episodes of upper airway collapse while sleeping.¹ It's estimated that about 25% of the US population is at high risk of developing OSA, and according a prospective, observational study performed by Finkel, et al., the estimated prevalence was 20% in adult population (18≥).² These numbers are expected to rise in the coming years mainly due to the obesity epidemic plaguing the US. Even with a high prevalence, it is estimated that up to 90% of OSA patients go undiagnosed, due to low awareness about OSA, lack of routine screening, and limited numbers of sleep study facilities.²

The primary diagnostic method of OSA is polysomnogram (PSG). A PSG is conducted at a sleep lab or sleep center and requires 24 hours of observation.³ During the sleep study several variables are measured, which include eye movement, brain activity, blood pressure, and heart rate. The PSG study also measures the number of apneas and hypopneas, as well as oxygen levels in the body. An apnea occurs when the complete cessation of airflow occurs for at least 10 seconds; whereas hypopnea is when there is a reduction of airflow but also includes either desaturation of oxygen of 3% to 4% or an arousal from sleep occurs. The apnea-hypopnea index or AHI is used to calculate if an individual has sleep apnea and the severity.³

Over time, persistent intermittent hypoxia and sleep fragmentation caused by OSA can affect the function of the brain and cardiovascular system as well as alter the body's metabolic balance. Three studies conducted between the 1990s to early 2000s found that patients with OSA were at a higher risk for developing many other chronic diseases such as congestive heart failure

(2.38 odds ratio compared to 1.13)⁴, hypertension (6.85 odds ratio for moderate-severe OSA compared to 0.89 for snoring)⁵, and type 2 diabetes (T2DM) (1.49,1.93,and 3.69 odds ratio for mild, moderate, and severe OSA respectively).⁶ Patients with undiagnosed and untreated OSA not only increase their risk of other diseases, but they also increased healthcare utilization and costs.⁷ A case-control study performed in Manitoba, Canada looked at healthcare costs and utilization records over a five year period from the OSA diagnoses date for 773 OSA adults. The study found that OSA patients spent on average \$1,912 compared to the control group who spent \$1,495 on healthcare related items such as office visits and medications. They also found that individuals who suffered from OSA had on average 36.7 physician visits versus the control group that had 29.9 visits.⁸

There is currently little information on the incidence of hypertension and T2DM among patients with OSA. The lack of information may partly be due to the difficulty in diagnosing individuals with OSA. In many cases the patient has been suffering from OSA for years before being correctly diagnosed. Some studies have reported that certain demographic factors such as BMI, gender, age, and OSA severity play a role in increasing one's risk of developing either hypertension or type 2 diabetes in people with OSA. Better understanding the relationship between hypertension and OSA as well as T2DM and OSA could assist with better diagnosis and management of OSA and other chronic diseases.

1.2 Purpose of Study

The primary purpose of this study is to estimate the association between OSA severity and incident hypertension and type 2 diabetes (T2DM). A secondary purpose is to examine whether

factors such as gender, age, BMI, or baseline co-morbidity are associated with incidence of T2DM or hypertension in patients with OSA.

Chapter 2: Literature Review

2.1 Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is characterized by repetitive airway obstruction due to the throat muscles intermittently relaxing during sleep.^{3,6,9} Individuals with OSA may experience excessive daytime sleepiness, snoring, observed episodes of breathing cessation during sleep, abrupt awakening with shortness of breath, awakening with dry mouth, sore throat, or chest pain, morning headaches, difficulty concentrating during the day, mood changes, and insomnia.^{3,6,9}

The primary method for diagnosis of OSA is laboratory full night polysomnography (PSG).^{3,9} PSG involves overnight monitoring of several physiological variables such as electroencephalography, eye movement, muscle tone, respiratory efforts, airflow, and oxygen saturation. During the monitoring, the number of apneas and hypopneas are counted. An apnea occurs when the complete cessation of airflow occurs for at least 10 seconds, and hypopnea is when there is a reduction of airflow but also includes either desaturation of oxygen of at 3% to 4% or an arousal from sleep occurs. The apnea-hypopnea index (AHI) is the total number of apneas and hypopneas per hour, and this is used as the basis for OSA diagnosis. The level of severity of OSA is graded using the commonly accepted clinical criteria: no OSA (AHI < 5), mild OSA (AHI ≥5 but less than 15), moderate OSA (AHI ≥15 but less than 30), and severe OSA (AHI ≥30).⁹

Treatment for OSA can differ depending on the severity. Lifestyle changes are the main recommendation for individuals with mild OSA.¹⁰ These changes could include losing weight, regular exercise, not drinking several hours before bed, smoking cessation, or choosing a sleeping position that is not on the back. If sleep doesn't improve or the individual has moderate to severe OSA other treatments such as devices or surgeries maybe recommended.¹⁰ The most common treatment for OSA is continuous positive airway pressure (CPAP). This therapy consists of a small machine that supplies a constant stream of steady air pressure through the nasal passageway.^{9,10} The constant stream of air will keep the upper airway open which prevents OSA and snoring.¹⁰ However many OSA patients find the CPAP machine uncomfortable, so adherence to it is small. In cases where the patient has trouble with the CPAP, the doctor may recommend the bilevel positive airway pressure (BPAP) machine. The BPAP delivers a preset amount of pressure when an individual breathes in and a different amount when the individual breathes out.¹⁰

When the aforementioned devices and lifestyle changes are ineffective in preventing OSA, the next step is surgery. Tissue can be surgically removed from the back of the mouth and top of the throat. Tonsils and adenoids are commonly removed during this surgery as well.¹⁰ Another option is maxillomandibular or jaw surgery. In this procedure, the upper and lower parts of the jaw are moved forward away from the rest of the facial bones. The space between the tongue and soft palate is enlarged, and the chances of airway obstruction are less likely. When all other treatments and surgeries have failed or an individual has life threatening OSA the doctor may recommend a tracheostomy. The surgeon would create an opening in the neck and insert a metal or plastic tube for breathing. This would bypass the throat preventing obstruction.¹⁰

Studies have found several risk factors that increase an individual's chances of developing OSA. The strongest risk factor is obesity. BMI, neck circumference, and waist-to-hip ratio have all shown a relationship between weight gain and OSA.^{11,12,13} Several studies have reported a relationship between obesity and OSA. A 2003 cross-sectional study of 690 adults taken from the Wisconsin Sleep Study by Young and colleagues reported that for adults, 60 years and younger, every point increase in BMI increased the odds of developing OSA is 1.14 (CI: 1.10-1.19).¹² Other risk factors included being middle aged (up to 65)¹⁴, male gender¹⁵, post-menopause¹⁶, craniofacial abnormalities¹⁷, upper airway anatomy abnormalities¹⁸, smoking¹³, alcohol consumption before bed¹⁹, and genetic predisposition¹³.

Three population-based longitudinal studies assisted with estimating the incidence of OSA (Table 1). In the Cleveland Family Study, the researchers found that the majority of the 286 subjects did not develop OSA after five years; however, 16% developed mild OSA, and 7.5% had moderate to severe OSA.⁶ Other studies have encountered similar results. The five-year follow-up of the Sleep Heart Health Study found that of the 2,968 participants 11.1% of men and 4.9% of women developed moderate to severe OSA.¹¹ The Wisconsin Sleep Cohort Study had a total of 690 subjects and after a four-year follow-up about 10.6% of subjects developed OSA.⁷

One of the largest population-based sleep studies, Wisconsin Sleep Cohort Study, estimated the prevalence of OSA as 2% in women and 4% of men in the general population. Other studies have yielded similar results. However, certain disorders have a higher prevalence such as heart disease, resistant and systemic hypertension, T2DM, and polycystic ovary syndrome to name a few.⁷ The increased prevalence of other disorders in OSA patients originated from the intermittent hypoxia and sleep fragmentation that OSA causes.²⁰ A consequence of intermittent hypoxia and sleep fragmentation is increased levels of oxidative

stress, low-grade inflammation, activation of the sympathetic nervous system, and deregulation of the hypothalamic-pituitary-adrenal axis.²⁰

2.2 Obstructive Sleep Apnea and Type 2 Diabetes

Studies over the years have been building evidence suggesting a relationship between OSA and diabetes. OSA and diabetes have similar risk factors such as obesity. However, once these factors have been accounted for, an independent relationship is still demonstrated.¹ The prevalence of T2DM in OSA patients is estimated in the range of 15-30 %, but depending on how the researchers define OSA or the study population the prevalence could be as high as 40%.¹ According to the American Diabetes Association, the prevalence of diabetes in the general US population is 9.3%.²¹

A cross-sectional study conducted by Priou, et al aimed at determining the association between OSA severity and glycated hemoglobin (HbA_{1c}), included 1,599 adults (475 females and 1,124 males) from western France from 05/15/2007 thru 11/30/2011.²⁹ A dose-response was found between individuals with a HbA_{1c} greater than 6% and OSA severity. There were 10.8% of patients with HbA_{1c} \geq 6% who had an AHI less than 5 whereas patients with an AHI over 50 were 34.2%.²⁹

Diabetes mellitus is a complex chronic metabolic disease characterized by high fasting blood glucose.²² This disease occurs when the pancreas cannot produce enough insulin, or the body cannot properly use the insulin produced.²³ Glucose is the basic unit of complex carbohydrates which is then broken down to be used for energy in the body. Excess glucose is stored as glycogen, in limited quantities, in fat cells around the body.²² The symptoms of diabetes are excessive excretion of urine, thirst, constant hunger, weight loss, vision changes, and

fatigue.²³ Type 2 diabetes (T2DM) is developed when the body can no longer effectively use the insulin it produces, because of insulin resistance.²²⁻²³ T2DM is mainly a result of excess body weight and physical inactivity and comprises 90% of diabetic cases worldwide.²³

Complications from diabetes are developed gradually over time and are seen more frequently in people who have had the condition for years or in people who have less controlled blood sugar. Excess sugar in the body causes damage to blood vessels in the body and as a result, many diabetics suffer from nerve, kidney, eye, and foot damage. Individuals with diabetes have also experienced an increased risk of developing cardiovascular disease, Alzheimer's disease, and hypertension.²³

As previously mentioned above, OSA causes two mechanisms, intermittent hypoxia and sleep fragmentation, which induces several concerns in the body. These concerns range from disorders such as sympathetic nervous system activation, oxidative stress, systemic inflammation, alterations in hormones, and activation of the hypothalamic-pituitary-adrenal axis. This process can lead to the development of insulin resistance which can progress into glucose intolerance and eventually diabetes.²⁴

A study was performed in 2009 that explored the relationship between OSA and insulin resistance, glucose intolerance, and T2DM. This cross-sectional study observed 118 non-diabetic subjects and conducted a PSG and glucose testing.³⁰ Of the 118 subjects, 11 subjects had missing sleep pattern information, 39 subjects had no OSA, 34 had mild OSA, 22 subjects had moderate OSA, and 23 subjects had severe OSA. Compared to normal subjects the reduction of insulin sensitivity for those with mild, moderate, and severe OSA was 26.7%, 36.5%, and 43.7% respectively.³⁰

The effect of CPAP therapy on insulin sensitivity is still unclear. Some studies found that subjects on CPAP therapy for at least three months had improved insulin sensitivity and metabolic control; while other studies found reduced HbA1c levels and body weight, but were unsure if the CPAP treatment or weight loss was the reason for the improved metabolic control.¹

2.3 Obstructive Sleep Apnea and Hypertension

It is common for individuals to have both OSA and hypertension. Studies have estimated that the prevalence of hypertension among OSA patients ranges from 30-70% while an estimated 30% of hypertensive patients have been undiagnosed.²⁵ In two large population-based studies, the odds of prevalent hypertension were twice as high in patients with OSA compared to patients without OSA (table 2). Both studies completed a four-year follow-up and adjusted for known confounders such as sex, BMI, and race.⁷

The first study was a population-based, cross-sectional study that included 1000 women and 741 men. The study was divided into two phases. The first phase consisted of telephone interviews conducted on 12,219 women and 4,364 men who were randomly selected from 2 counties in southern Pennsylvania (Dauphin and Lebanon). They utilized a questionnaire that included questions regarding demographics and risk factors for sleep apnea. The second phase randomly selected subjects from the telephone interview phase in the sleep laboratory for assessment of the presence of sleep apnea. Individuals selected for the second phases were asked to provide a comprehensive sleep history, complete physical examination, and psychometric assessment of cognitive and psychological functions. The researchers found a dose-response pattern among the prevalence of hypertension and three groups; moderate or severe sleep apnea,

mild sleep apnea, and snoring. The odds ratios were 6.8 (2.02-26.36) for moderate or severe sleep apnea, 2.3 (1.43-3.61) for mild sleep apnea, and 1.56 (1.09-2.20) for snoring.⁵

The second population-based, cross-sectional study was conducted using individuals from the Sleep Heart Health Study. Prior to the baseline home visit, the participants were administered a sleep habits questionnaire that included snoring history, sleep apnea awareness, sleep apnea treatment, and sleepiness. The home visit included a brief health interview, valuation of current medications, blood pressure measurements, and a full unattended PSG. The results found that the odds of hypertension among participants with high AHI (≥ 30 per hour) compared to participants with low AHI (≤ 1.5 per hour) was 2.27 (1.76-2.92).²⁸

Hypertension (also called high blood pressure) is a condition where the blood vessels have consistently raised pressure.²⁶ When a heart beats, it creates a force that pushes oxygen-containing blood through the body. Blood pressure is made up of a combination of force it takes for the heart to pump blood out of the heart and the other force is the rest period between heart beats. Hypertension is measured using two numbers: systolic and diastolic pressure. Systolic pressure is the pressure in the arteries when the heart contracts (heartbeat) while diastolic pressure measures the artery pressure when the heart is at rest (between beats). The optimal range for blood pressure is a systolic pressure of less than 120 and a diastolic pressure of less than 80. You are considered to have hypertension is diagnosed when a systolic pressure of 140-159 or diastolic pressure is 90-99. This disease is called the “silent killer” because it has no symptoms unless an individual goes into hypertensive crisis. Hypertensive crisis is when an individual has a systolic pressure of 180 and higher or a diastolic pressure of 110 and higher.²⁶ Blood pressure at that level can lead to a stroke in the individual.²⁶

A type of hypertension that is a cause for concern is resistant hypertension. Resistant hypertension is when a patient can't control their blood pressure regardless of the use of a diuretic and, at least, two other blood pressure medications. The number of people who suffer from resistant hypertension is unknown; however, recent clinical trials estimate the prevalence around 10%.²⁷

When hypertension goes undiagnosed or uncontrolled, it can cause severe damage to the blood vessels and organs. This condition can lead to heart attacks, enlargement of the heart, and heart failure. Blood vessels are more likely to clog and burst due to the bulges and weak spots the pressure creates. The pressure can also cause blood to leak into the brain, which can increase an individual's risk of a stroke. Hypertension can also increase the risk of blindness, cognitive impairment, kidney failure, and rupture of blood vessels.²⁷

Blood pressure is affected by OSA because it stops an individual from breathing. Anytime breathing is disturbed it causes oxygen levels in the body to drop, and the receptors in the brain are alerted. As a result, the brain sends signals to the nervous system, and the blood vessels constrict so that oxygen is primarily flowing to the heart and brain. This process can carry over into the daytime while OSA patients are awake. The mechanisms that are triggered at night by the OSA persist throughout the day and eventually will develop in hypertension.²⁵

Chapter 3: Methods

3.1 Study Design and Study Setting

This retrospective cohort study examined Kaiser Permanente Georgia (KPGA) adults ≥ 18 years of age who were examined at the Sleep Disorder Center of Georgia between the years 2000-2005 and who were initiated on continuous positive airway pressure (CPAP) therapy

during this period (N=426). Members were followed until December 31, 2010 to determine if they had incident T2DM or hypertension by examining diagnoses in computerized medical records.

3.2 Participants

Subjects in the study were adults ($18 \geq$) Kaiser Permanente members who had been seen in at the Sleep Disorder Center of Georgia, tested for OSA, and prescribed CPAP therapy.

3.3 Variables

The primary outcome variables were: the incidence of T2DM, and the incidence of hypertension. Incidence of T2DM was defined as a diagnosis date following the CPAP initiation date. Incidence of hypertension is defined similarly. Diagnosis is determined through evidence of disease using relevant diagnosis codes, abnormal test results, or pharmacy dispensings.

3.4 Data Management

This study links a CPAP database acquired from the Sleep Disorder Center of Georgia with several KPGA databases: membership enrollment, diabetes registry, and hypertension registry. All datasets can be linked by the health record number (HRN). The CPAP database also contains the date of initiation for CPAP and the level of OSA severity classification. The membership enrollment database serves as the source of date of birth, gender, and enrollment duration prior to CPAP initiation (number of member months in the 12-months prior to the month of CPAP initiation), and a date of disenrollment (if any) following CPAP initiation until 12/31/2010. The diabetes and hypertension registries are the source of the dates of initial diagnosis (using KPGA registry criteria) of T2DM or hypertension.

3.5 Study Sample

The CPAP dataset included 719 individuals. The event and comparator numbers of patients decreased as additional inclusion and exclusion criteria were imposed (Figure 1). Twelve months of observation (KPGA enrollment) prior to the month of the CPAP initiation month were required to decrease the likelihood that a patient had T2DM or hypertension prior to KPGA enrollment because the member was not enrolled for a sufficient period of time to be entered into the diabetes or hypertension registries (which require visits with diagnosis codes, abnormal test results, or pharmacy dispensing for entry into the registries).

3.6 Statistical Methods

Individuals were followed through 12/31/2010. Separate analyses were conducted for incident T2DM or incident hypertension. Within each analysis, the endpoints for Kaplan-Meier analysis were defined by: incident T2DM or hypertension prior to 12/31/2010 (event), disenrolled from KPGA prior to 12/31/2010 (censored), or end of study at 12/31/2010 (censored).

The event time was computed from the CPAP initiation date to the incidence date of either T2DM or hypertension. The censoring dates were computed from the CPAP date to date of disenrollment, after seven years of enrollment, or 12/31/2010-which ever occurred first. Both the incident T2DM group and the incident hypertension group were stratified by severity of OSA, gender, age group, disease prevalence, and BMI. A log rank test was conducted for each stratified analysis to determine if the risk of incident disease differed by OSA severity, gender, age group, comorbid disease, and BMI. A multivariable Cox proportional hazard model was also estimated.

Chapter 4: Results

4.1 Study Population

A total of 719 patients were diagnosed with OSA during the study period. Of the 719, we excluded 103 because they were not enrolled with KPGA for at least a year prior to CPAP initiation date. The OSA severity group had two observations missing. In the remaining 614 patients, 350 (57%) had hypertension before OSA diagnosis date and 125 (20%) had T2DM before OSA diagnosis (Figure 1). Therefore, 264 patients were eligible for the analysis of incident hypertension and 489 patients were eligible for the analysis of incident T2DM.

4.2 Descriptive Data

Among patients with diagnosed OSA (n=614, 60.1% (n=369) were male, the median age was 49 years (IQR 49-56), and 27.0% (n=166) were morbidly obese (Table 3). At time of OSA diagnosis, 42.5% (n=261) of patients had severe OSA, 28.5% (n=175) had moderate OSA, and 29.0% (n=178) had mild OSA. Compared to patients with mild OSA, those with severe OSA were more likely to be morbidly obese (38.7% vs. 19.7%), older (median 50 vs. 48), male (67.8% vs. 46.6%), and have both comorbid T2DM (26.1% vs. 18.0%) or comorbid hypertension (62.8% vs. 48.9%) at the time of OSA diagnosis (p-value <0.05 for all comparisons).

4.3 Incident Hypertension

Table 2 shows how demographic factors differ between the incident and non-incident hypertension group. Of the 265 patients without prevalent hypertension at CPAP initiation, 126 patients developed hypertension (incident hypertension) and 140 did not develop hypertension (non-incident hypertension). In the incident hypertension group, 33.6% (42 of 125) had mild OSA, 28.8% (36 of 125) had moderate OSA, and 37.6% (47 of 125) had severe OSA. Patients in

the non-incident hypertension group had 35% (49 of 140) mild OSA, 29.3% (41 of 140) had moderate OSA, and 35.7% (50 of 140) had severe OSA ($p=0.95$). The incident hypertension group had more obese 56.5% (70 of 124) compared to the not obese 24.2% (30 of 124) and morbidly obese 19.4% (24 of 124) groups ($p=0.05$). The median age for both incident and non-incident group was 44. The incident group had more males 60.8% (76 of 125) than females 40% (50 of 125; $p=0.47$). The non-incident hypertension group also had more males 69.3% (97 of 140) than females 30.7% (43 of 140; $p=0.47$). The incident hypertension group had 8% (10 of 125) of patients that had comorbid T2DM and 92% (115 of 125) did not have comorbid T2DM. In the non-incident hypertension group 3.6% (5 of 140) had comorbid T2DM and 96.4% (135 of 140) did not have T2DM ($p=0.12$).

A Kaplan-Meier survival curve was calculated using time to hypertension diagnosis and severity of OSA (Graph 1). According to the survival curve, patients that suffered from severe OSA developed hypertension more quickly following CPAP initiation compared to patients with moderate and mild OSA. The p -value for the log rank test was 0.1. A crude and adjusted Cox proportional hazard model was estimated for incident hypertension (Table 3). Mild OSA was used as the referent group in both calculations. Patients who had moderate OSA had a 2% lower risk of developing hypertension in the future (hazard ratio [HR]: 0.98, CI: 0.63-1.53). Also, patients with severe OSA had a 48% (HR: 1.48, CI: 0.98-2.25) increased risk of developing hypertension in the future compared to patients with mild OSA. Once the hazard ratios were adjusted using BMI and comorbid T2DM, the risk of incident hypertension increased slightly for moderate OSA by 4% (adjusted [aHR]: 1.04 CI: 0.66-1.64) and decreased by 13% for severe OSA (aHR: 1.35 CI: 0.88-2.06).

4.4 Incident T2DM

In the T2DM sample (n=491), 80 developed diabetes (incident T2DM) and 409 did not develop diabetes (non-incident T2DM). Of the 80 patients who developed T2DM, 21.3% (17 of 80) had mild OSA, 26.2% (21 of 80) had moderate OSA, and 51.3% (41 of 80) had severe OSA while patients who did not develop T2DM had 31.5% (129 of 409) who had mild OSA, 31.5% (129 of 409) had moderate OSA, and 37.2% (152 of 409) had severe OSA (p=0.04). The incident diabetes group had 13.8% (11 of 80) of patients who were not obese, 47.5% (38 of 80) who were obese, and 38.8% (31 of 80) morbidly obese. While patients in the non-incident T2DM group had 27.5% (111 of 403) who were not obese, 50.4% (203 of 403) who were obese, 22% (89 of 403) who were morbidly obese (p<0.01). The median age was 50 and 47 for the incident and non-incident T2DM groups respectively (p=0.13). Both groups had more men than women. In the incident T2DM group 68.8% (55 of 80) had comorbid hypertension while 31.2% (25 of 80) did not have comorbid hypertension. The non-incident group had 45% (185 of 411) with comorbid hypertension and 55% (226 of 411) did not have comorbid hypertension (p=<0.01). (Table 2)

The Kaplan-Meier survival curve was calculated with time to T2DM (in days) based on OSA severity. (Graph 2) The graph shows that patients with severe OSA developed T2DM more quickly following CPAP initiation than patients with mild or moderate OSA. The p-value for the log rank test was 0.03. A crude and adjusted Cox proportional hazard model was estimated for incident T2DM (Table 3). Mild OSA was used as the referent group in both calculations. Patients with moderate OSA and severe OSA were at a 23% (HR: 1.23 CI: 0.65-2.33) and 98% (HR: 1.98 CI:1.12-3.49) increased risk of developing T2DM in the future. After adjusting for BMI and

comorbid hypertension, the hazard ratio decreased by 12% (aHR: 1.12 CI: 0.59-2.13) for patients with moderate OSA and 49% (aHR: 1.49 CI: 0.83-2.67) for patients with severe OSA.

Chapter 5: Discussion

This study provides some evidence that there is an association between incident T2DM and OSA severity. The Cox Proportional hazard models did not show a statistically significant association, however the Kaplan-Meier curve did suggest a statistically significant association between risk of incident T2DM and severe OSA at the conventional level of $p \leq 0.05$. The findings from this study did not indicate an association between incident hypertension and OSA severity. The hazard models and Kaplan-Meier curve did not indicate a statistically significant association between incident hypertension and OSA severity at the conventional level.

One primary reason OSA affects T2DM more than hypertension could be the effect it has on the hypothalamic-pituitary-adrenal (HPA) axis. Studies have found that poor sleep quality and sleep disorders like OSA can increase the level of individual stress.³¹ This exposure to stress can increase the release of glucocorticoids by the HPA, and prolonged activation of the HPA can cause harmful changes. These changes can affect puberty, stature, body composition which includes obesity, metabolic syndrome, and T2DM.³¹

There are several limitations to this study. One limitation is the lack of information on CPAP adherence of the patients. Studies that look at the effects of CPAP therapy on conditions such as hypertension and T2DM among OSA patients have conflicting findings. Some studies have found a decrease in blood pressure and glucose intolerance when CPAP is regularly used^{6,32}, but other studies do not get similar results^{33,34}. This is important because CPAP therapy is found to be cumbersome and uncomfortable so more OSA sufferers decide not to use the

machine. The results could be skewed the results towards the null hypothesis because patients with more severe OSA may adhere to CPAP therapy more than other which could reduce their chances of developing hypertension or T2DM. Another limitation is the process by which we created the study sample. The patients in this study had to be referred to the sleep clinic by their general physician, complete an overnight polysomnography test, and then placed on CPAP therapy. These patients had to be relatively compliant to take CPAP therapy, so these patients were more likely to be adherent to not only their CPAP therapy but also any other recommendations the doctor advises. We have no information on the patients that were referred for a sleep study and never completed it. This limitation could skew the results towards the null as well since these patients may try to take better care of themselves and decrease their risk of other diseases.

OSA is a disorder that goes largely undiagnosed and untreated in many people. This comes from a lack of knowledge about the disorder and the increased risk it puts people in. Even though the findings in this study did not find an association between hypertension and OSA severity and a plausible association between T2DM and OSA severity, there were still a large number of patients that developed both hypertension (47%) and T2DM (16%). This shows that there is some association between them even if it is based on severity. More research needs to be done to understand better the relationship between the diseases. There also needs to be more research in if and how CPAP therapy can decrease the risk of developing hypertension and T2DM

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Figures, Tables, and Graphs

Study Name	Number of Participants	Years between Follow-Up	Incidence	Reference
Wisconsin Sleep Cohort Study, 2000	286	5	16%-Mild OSA 7.5 Moderate to Severe OSA	Peppard et al., 2000
Cleveland Family Study, 2003	2,968	5	11.1%- Males 4.9%- Females	Tishler et al., 2003
Sleep Heart Health, 2005	690	4	10.6%- Mild to Severe	Newman et al., 2005

Table 2. Studies on Obstructive Sleep Apnea and Incident Hypertension		
Study	Number of Participants	Odds Ratios (CI)
Bixler et al, 2000	1741 1000-Females 741-Males	6.8 (2.02-26.36)- Moderate to Severe OSA 2.3 (1.43-3.61)- Mild OSA 1.56 (1.09-2.20)- Snoring
Nieto et al, 2000	6,132 52.8%-Females 47.2%-Males	2.27 (1.76-2.92)

Figure 1. Flow chart of study sample selection

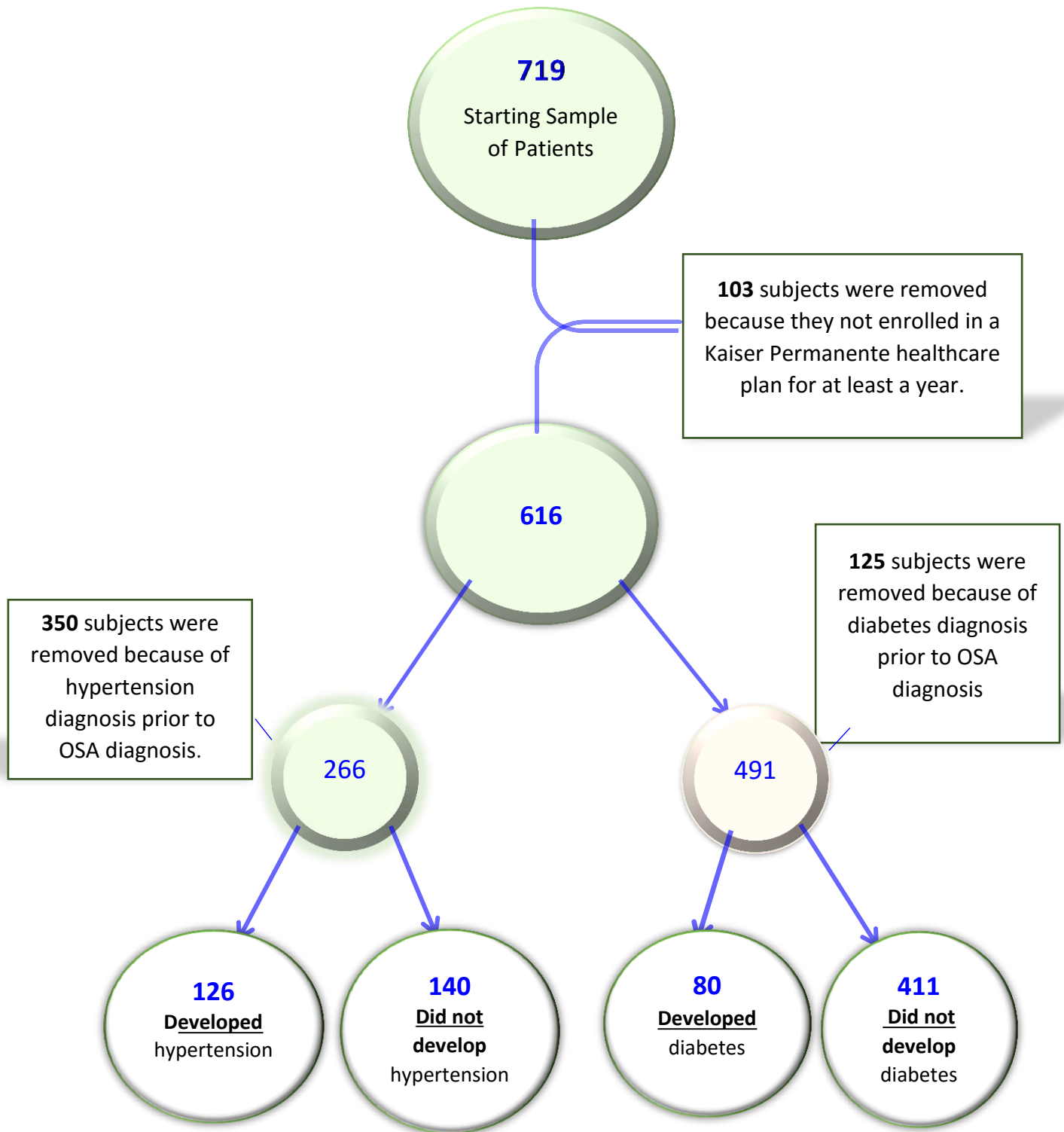


Table 3. Baseline patient characteristics and obstructive sleep apnea severity classification					
Sample Size N=614		Mild (n=178)	Moderate (n=175)	Severe (n=261)	p-value
BMI Group	Not Obese	52(30.06%)	41(23.84%)	42(16.34%)	<0.01
	Obese	86(49.71%)	101(58.72%)	114(44.36%)	
	Morbidly Obese	35(20.23%)	30(17.44%)	101(39.30%)	
Age		Median: 48 IQR: 48-56	Median: 48 IQR: 48-54	Median: 50 IOR: 50-56	0.03
Gender	Female	95(53.37%)	66(37.71%)	84(32.18%)	<0.01
	Male	83(46.63%)	109(62.29%)	177(67.82%)	
Prevalent Diabetes	Yes	32(17.98%)	25(14.29%)	68(26.05%)	<0.01
	No	146(82.02%)	150(85.71%)	193(73.95%)	
Prevalent Hypertension	Yes	87(48.88%)	98(56.00%)	164(62.84%)	0.01
	No	91(51.12%)	77(44.00%)	97(37.16%)	

*OSA level is categorized as the following: Mild: 5-14AHI, Moderate: 15-29AHI, and Severe: ≥ 30 . BMI Group: Not Obese: 18.5-29.9, Obese: 30-39.9, Morbidly Obese: ≥ 40 . OSA severity had two individuals missing and BMI had six missing individuals.

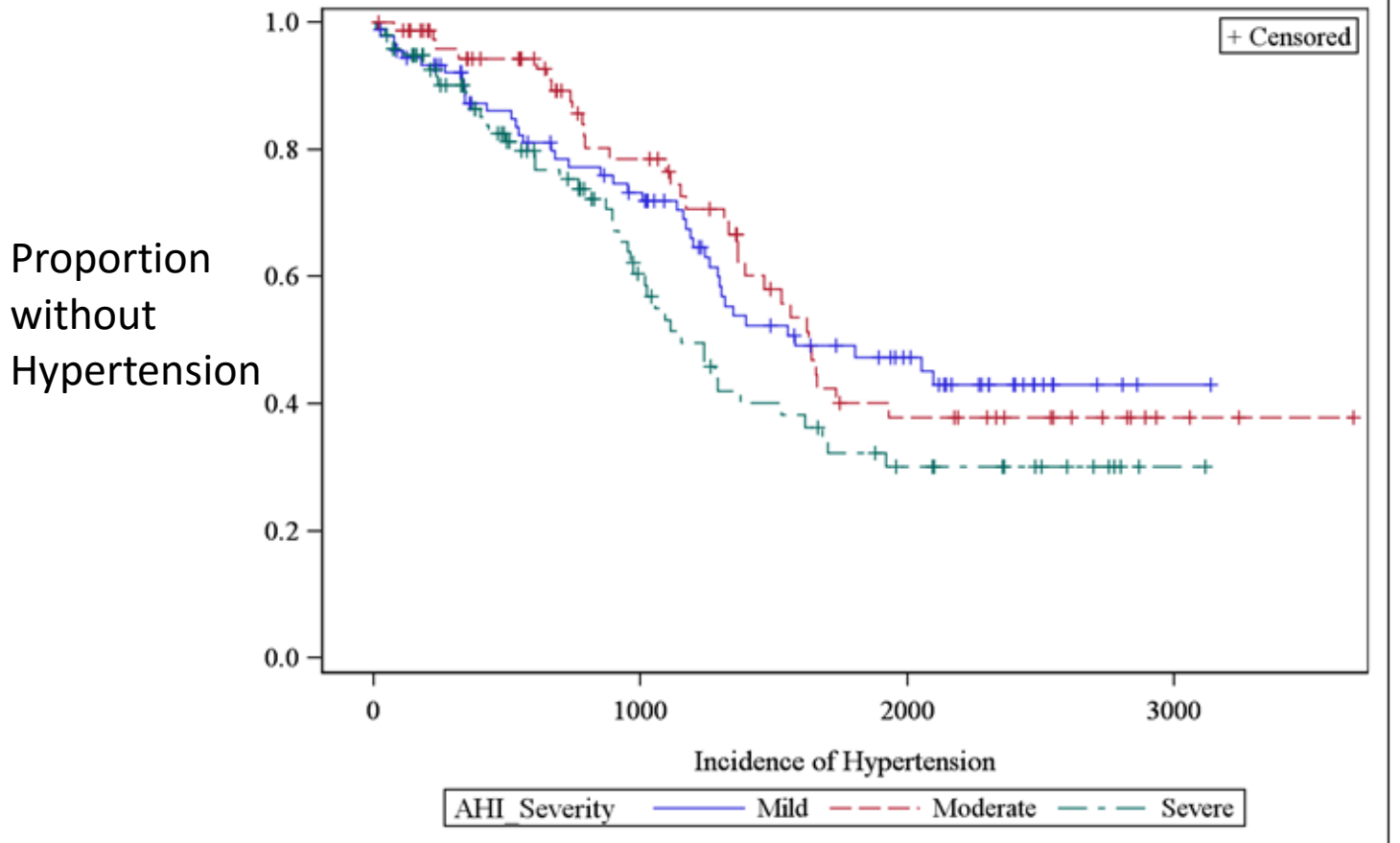
		Incident Hypertension (HTN) Sample (N=265)			Incident Type 2 Diabetes (DM) Sample (N=489)		
		With Incident HTN	Without Incident HTN	P-value	With Incident DM	Without Incident DM	P-value
N of Patients		125 (47.17%)	140	--	80 (16.36%)	409	--
OSA Level	Mild	42(34.75%)	49(34.02%)	0.95	17(21.52%)	129(31.46%)	0.04
	Moderate	36(27.12%)	41(30.61%)		21(26.58%)	129(31.47%)	
	Severe	47(38.14%)	50(35.37%)		41(51.90%)	152(37.07%)	
BMI Group	Not Obese	30(22.41%)	51(37.76%)	0.05	11(13.92%)	111(27.36%)	<0.01
	Obese	70(56.90%)	59(44.06%)		38(48.10%)	203(50.50%)	
	Morbidly Obese	24(20.69%)	26(18.18%)		31(37.98%)	89(22.14%)	
Age		Median:44 IQR: 17	Median:44 IQR:14	0.47	Median:50 IQR:12	Median:47 IQR:15	0.13
Gender	Female	50(41.38%)	43(29.37%)	0.13	36(45.57%)	151(36.59%)	0.16
	Male	75(58.62%)	97(70.63%)		44(54.43%)	260(63.41%)	
Comorbid Disease	Yes	10 (8.62%)	5(3.50%)	0.12	55(68.35%)	185(45.12%)	<0.01
	No	115 (91.38%)	135(96.50%)		25(31.65%)	226(54.88%)	

* OSA level is categorized as the following: Mild: 5-14AHI, Moderate: 15-29AHI, and Severe:≥30. BMI Group: Not Obese: 18.5-29.9, Obese: 30-39.9, Morbidly Obese: ≥40. Comorbid disease for incident hypertension sample is T2DM. Comorbid disease for T2DM sample is hypertension. OSA severity had two individuals missing and BMI had six missing individuals.

Table 5. Crude and Adjusted Hazard Ratios for Incident Type 2 Diabetes and Hypertension by Obstructive Sleep Apnea Severity						
	Incident DM			Incident HTN		
	Median Time (Years) to Incident DM	Crude Hazard Ratio	Adjusted Hazard Ratio	Median Time (Years) to Incident HTN	Crude Hazard Ratio	Adjusted Hazard Ratio
Mild OSA	Median:3.01 IQR:2.79	1.00	1.00	Median:2.46 IQR: 2.59	1.00	1.00
Moderate OSA	Median:2.17 IQR: 1.25	1.23(CI:0.65-2.33)	1.12(CI:0.59-2.13)	Median: 3.17 IQR: 2.20	0.98(CI: 0.63-1.53)	1.04(CI:0.66-1.64)
Severe OSA	Median:2.57 IQR: 3.42	1.98(1.12-3.49)	1.49(CI:0.83-2.67)	Median: 2.38 IQR: 2.05	1.48(CI:0.98-2.25)	1.35(CI:0.88-2.06)

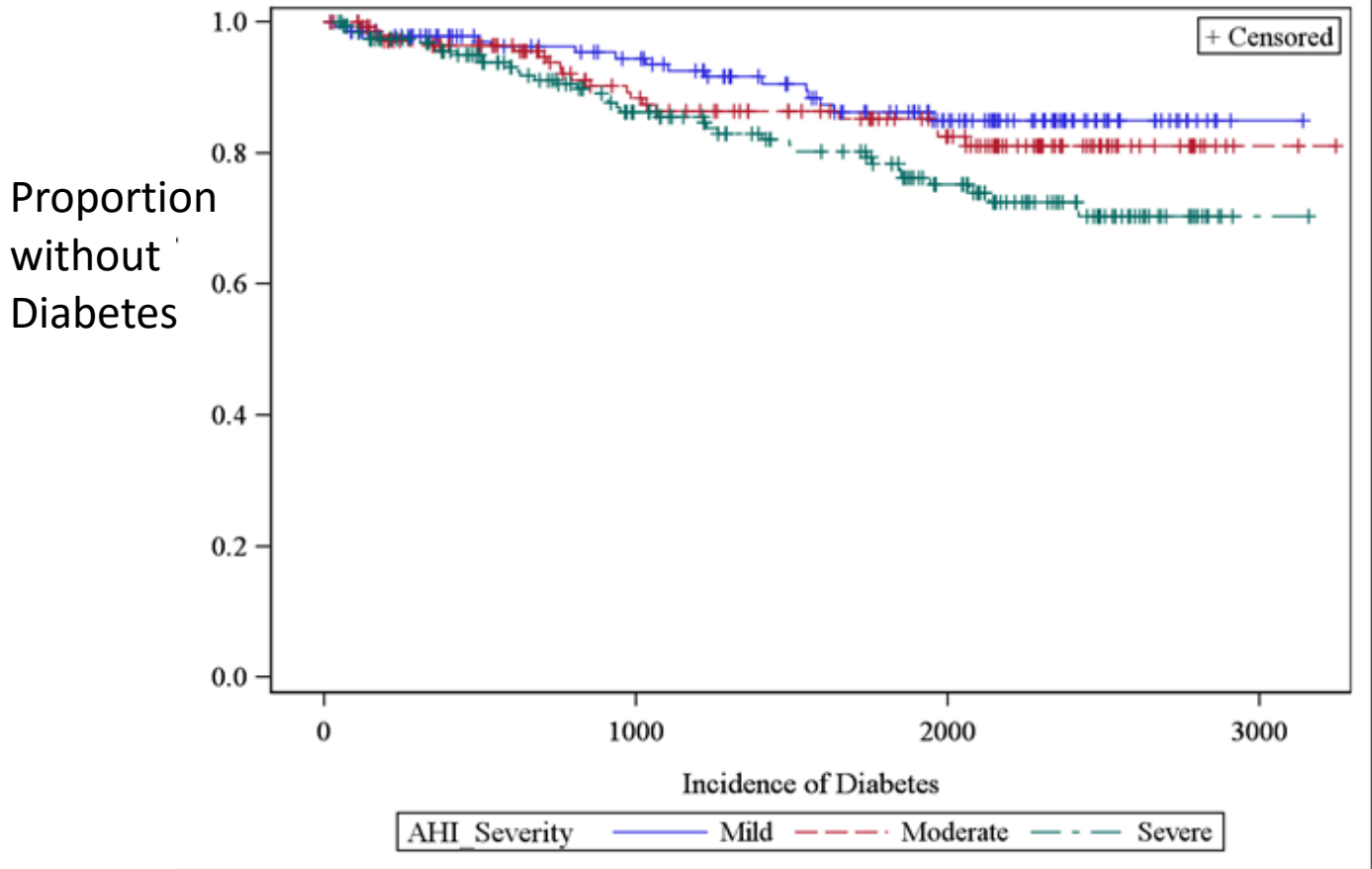
* Adjusted ratios were calculated using BMI and prevalent comorbidity. OSA severity had two individuals missing. OSA level is categorized as the following: Mild: 5-14AHI, Moderate: 15-29AHI, and Severe: ≥ 30 .

Graph 1. Kaplan-Meier Survival Curve for Incident Hypertension and Obstructive Sleep Apnea Severity



Log-Rank Test= 0.1

Graph 2. Kaplan-Meier Survival Curve for Incident Type 2 Diabetes and Obstructive Sleep Apnea Severity



Log-Rank Test=0.03