PREVALENCE OF AND FACTORS ASSOCIATED WITH OBSTRUCTIVE SLEEP APNEA IN A COHORT OF ADULTS WITH LONG DURATION TYPE 1 DIABETES MELLITUS

by

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ABSTRACT

Chronic health conditions like diabetes and sleep disorders have been increasing. Previous research showed that diabetes and sleep disorders are interrelated. The majority of studies examining this relationship focused on type 2 diabetes. Although a relationship between sleep disorders and type 1 diabetes (T1D) has been studied, investigations have been limited to youth and small samples. We, therefore, aimed to assess the prevalence, overall and gender-specific, and correlates, of obstructive sleep apnea (OSA) risk in an adult cohort with long-standing T1D.

A total of 170 individuals with T1D attending the 25-year follow-up of the Pittsburgh Epidemiology of Diabetes Complications study who completed an OSA screening tool, the Berlin Questionnaire (BQ), were included in this cross-sectional analysis. Those scoring positively on the BQ and/or reported a previous OSA diagnosis were classified as being at high OSA risk.

The OSA risk prevalence was 25.9% (25.0% among men, 26.6% among women). High versus low-OSA-risk individuals differed univariately with respect to markers of obesity, systolic blood pressure, estimated glucose disposal rate, lipid profile, and smoking history, although no differences were observed in hemoglobin A1c. In the final multivariable model, adjusting for sex and diabetes duration, body mass index (BMI) (directly, p=0.01), high-density lipoprotein (HDL) (inversely, p=0.03), and smoking history (directly, p=0.04) correlated with OSA risk. In gender-specific analyses, adjusting for diabetes duration, BMI (directly, p=0.007) and HDL (inversely,

p=0.03) were also associated with OSA risk in women, while diastolic blood pressure (p=0.01) and smoking history (p=0.04) were positive OSA correlates in men.

Our findings suggest that the prevalence of high OSA risk in adults with long-standing T1D is comparable to that in the general population. Given that both OSA screening tools and treatment are widely available, identifying high OSA risk among individuals already burdened with a serious chronic disease is of public health importance. Indeed, modifiable risk factors were independently associated with OSA risk in this study, suggesting that the adoption of a healthier lifestyle may reduce OSA risk in T1D, improving the wellbeing and reducing the subsequent risk of further complication development. Future prospective cohorts should be conducted to explore this hypothesis.

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LIST OF ABBREVIATIONS

AHI = Apnea-hypopnea index

BMI = Body mass index

BQ = Berlin Questionnaire

CAD = Coronary artery disease

CI = Confidence interval

CPAP = Continuous positive air pressure

DBP = Diastolic blood pressure

EDC = Epidemiology of Diabetes Complications

eGDR = Estimated glucose disposal rate

ESRD = End-stage renal disease

HbA1c = Hemoglobin A1c

hCAD = Hard coronary artery disease

HDLc = High-density lipoprotein cholesterol

HTN = Hypertension

LDLc = Low-density lipoprotein cholesterol

OR = Odds ratio

OSA = Obstructive sleep apnea

SBP = Systolic blood pressure

T1D = Type 1 diabetes

WHR = Waist to hip ratio

WHTR = Waist to height ratio

1.0 INTRODUCTION

Along with the changing patterns of modern lifestyle that entail being more efficient but less active and being more aware of healthy eating but having less time to prepare healthy foods, comes the rise of chronic diseases. For instance, burdensome public health conditions such as diabetes and sleep disorders continue to rise and contribute to decreased quality of life and increased morbidity and mortality. In 2014, the Centers for Disease Control and Prevention estimated that 29.1 million Americans, or 9.3% of the population, had diabetes [1]. This figure is more than 2 times higher than the prevalence rate from 2000 (4.4%) and more than 3 times higher than the 1990 prevalence rate of 2.7% [2]. Diabetes is accompanied by other chronic disorders such as heart disease, stroke, hypertension, kidney disease, and blindness, among many others, and individuals who suffer from this chronic condition are approximately two times more likely to experience premature death in comparison to diabetes-free individuals of similar age [3]. Indeed, recent estimates suggest that diabetes is now the 7^{th} leading cause of death in the United States [3]. Due to its widespread prevalence and debilitating impact, diabetes has become a national health care priority and the importance of addressing this serious public health condition has been well recognized.

In 2006, the Institute of Medicine estimated that 50-70 million of the U.S. adults had chronic sleep and wakefulness disorders [4]. Similarly to diabetes, an increasing trend in the prevalence of sleep disorders has also been observed among American adults. For instance, according to the National Sleep Foundation's 2001 *Sleep in America* Poll, the second most

common sleep disorder in the U.S., obstructive sleep apnea (OSA), was diagnosed among 5% of the randomly selected, nationally representative American adults [5]. This figure had almost doubled to 9% in the later conducted 2008 *Sleep in America* Poll [6]. Sleep apnea may be an even greater problem than these figures suggest, given that 75-80% of moderate or severe cases appear to be undiagnosed [7]. Furthermore, sleep disorders have also been linked to other health related conditions including hypertension, obesity, insulin resistance, cardiovascular disease, and impotence leading to decreased quality of life as well as to increased mortality [8].

Interestingly, investigators have suggested that these two chronic conditions, diabetes and sleep disorders, are interrelated. Thus, recent large prospective studies suggested that sleep disorders may contribute to the risk of developing diabetes [9-12]. Conversely, it has also been suggested that diabetes complications may contribute to the development of sleep impairments [13-15]. Individuals suffering from sleep disorders often experience apnea, hypopnea, hypoxia, and frequent arousals during sleep. This type of disturbed breathing can lead to increased insulin, insulin resistance, and presence of the metabolic syndrome, and therefore, contribute to the development of diabetes [16]. Furthermore, cortisol and catecholamines, hormones regulated by sleep, can elevate blood glucose when sleep is disturbed [16]. Chronic sleep deprivation may therefore lead to an increase in hemoglobin A1c. On the other hand, diabetes symptoms and complications, such as nocturia, hypoglycemia, or pain due to neuropathy, may keep individuals with diabetes awake at night and disturb their sleep [16]. Until this vicious cycle is broken by prevention or treatment, it will continue to interfere with the lives of individuals suffering from diabetes and/or sleep disorders.

The majority of studies that have linked sleep disorders with diabetes have focused on type 2 diabetes mellitus [9-15]. Although a relationship between sleep disorders and type 1 diabetes

mellitus has been studied, most of the studies conducted to the present date are limited to youth [17-18, 20-21] and small samples [17-22]. Thus, the aim of our study was to describe the prevalence of OSA risk in a cohort of adult individuals with long standing type 1 diabetes. We further aimed to determine factors associated with OSA risk in this cohort and specifically, whether lifestyle factors (e.g. obesity), diabetes related factors (e.g. glycemic control), and diabetes complications status (e.g. coronary artery disease) differed among individuals at high OSA risk and those with normal sleep patterns.

2.0 DIABETES MELLITUS

Diabetes mellitus is a group of chronic metabolic disorders marked by high blood glucose levels (i.e. hyperglycemia) that can cause serious health conditions such as heart disease, stroke, kidney failure, and blindness [1]. This complex disorder of carbohydrate, fat, and protein metabolism is typically a result of deficiency or lack of insulin secretion by the beta cells of the pancreas or a result of insulin resistance [23]. Individuals suffering from diabetes are often diagnosed after seeking medical attention due to clinical symptoms such as excessive thirst, hunger, and urination [23]. Two most commonly recognized forms of diabetes are type 2 and type 1 diabetes mellitus.

2.1 TYPE 2 DIABETES MELLITUS

Type 2 diabetes, formerly known as the non-insulin dependent diabetes mellitus, is the most common form of diabetes around the world. It is responsible for 90-95% of all diagnosed diabetes cases among adults [1]. This chronic condition is marked by the body's ineffective use of insulin (i.e. a hormone responsible for controlling blood glucose) [1]. The onset of the disorder is typically gradual. Early in the disease process, the pancreas usually produces enough insulin, but the cells in the muscle, liver, and adipose tissue cannot utilize it effectively (i.e. insulin resistance) [1]. Eventually, insulin production significantly decreases or completely ceases. This form of diabetes used to be primarily associated with older age, but it is now seen among children and youth as well, as the rates of overweight and obesity, the disease's major risk factors, have been increasing in those age groups [1]. Type 2 diabetes is highly related to lifestyle behaviors that lead to excess

body weight, such as physical inactivity, high-fat, and high-carbohydrate diet [1]. Importantly, a large multi-center clinical trial in the United States (Diabetes Prevention Program) demonstrated that the onset of type 2 diabetes can be prevented with lifestyle improvements or with use of oral antidiabetic medications (i.e. metformin) [24]. Other risk factors associated with this chronic metabolic disorder are familial diabetes history, history of gestational diabetes, and ethnicity (e.g. African Americans, American Indians, and Hispanics).

2.2 TYPE 1 DIABETES MELLITUS

Formerly recognized as the insulin-dependent diabetes mellitus, type 1 diabetes encompasses around five percent of all diagnosed diabetes cases [1]. This form of diabetes was previously known as juvenile-onset diabetes as its diagnosis most frequently occurs in children and youth [1]. However, type 1 diabetes can appear at any age. This autoimmune chronic condition develops when the immune cells attack and destroy insulin-producing beta cells in the pancreas, leading to the cessation of insulin secretion [23]. As a result, individuals suffering from type 1 diabetes need external insulin to survive. Although, type 1 diabetes has been linked to different genetic and environmental factors such as human leukocyte antigen genes and viral infections [23], the exact cause of the disease is still unknown. In addition, no known ways currently exist to prevent or cure type 1 diabetes mellitus.

3.0 OBSTRUCTIVE SLEEP APNEA

OSA, the second most common sleep disorder in the US after insomnia [6], is characterized by loud snoring, witnessed breathing pauses, chocking or gasping during sleep, insomnia, and daytime sleepiness. Individuals suffering from OSA exhibit complete or partial cessation of airflow as a result of upper airway collapse that lasts at least 10 seconds (i.e. apnea) [25]. Another major characteristic of OSA is hypopnea defined as a reduced airflow to the lungs by at least 30% that lasts a minimum of 10 seconds and is associated with a four percent oxygen desaturation, or a reduced airflow to the lungs by at least 50% that lasts a minimum of 10 seconds and is either associated with a three percent oxygen desaturation or an arousal from sleep [25]. Polysomnography (i.e. sleep study) is the gold standard for diagnosing OSA. Severity of OSA is measured by the average number of apneas and/or hypopneas per hour of sleep and defined by the apnea-hypopnea index (AHI) [25]. Individuals with the AHI between five and 15 events per hour are thought to suffer from mild OSA [25]. Those with the AHI between 15 and 30 events per hour are categorized as having moderate OSA [25]. Finally, individuals with the AHI greater than 30 events per hour suffer from severe OSA [25]. Common risk factors that have been associated with the development of OSA are obesity, central body fat distribution, large neck circumference, 40 to 70 years of age, male gender, menopause, and ethnicity (e.g. African American) [25]. Furthermore, chronic health conditions such as hypertension, coronary heart disease, stroke, and type 2 diabetes have either been shown to frequently coexist with OSA or to be adverse consequences associated with it [25].

3.1 OBSTRUCTIVE SLEEP APNEA AND TYPE 2 DIABETES MELLITUS

As it has been previously stated, recent studies have found that sleep disorders may contribute to the development of type 2 diabetes [9-12], while diabetes complications may contribute to the development of sleep impairments [13-15]. Type 2 diabetes and OSA share obesity as a major risk factor, which might partially explain their inter-relationship and high concurrence. In addition, both conditions are also marked with insulin resistance [26]. The higher prevalence of OSA among individuals with type 2 diabetes [27] than in the general population warrants healthcare professionals to evaluate the risk of OSA among the diabetes population, but also to evaluate the risk for type 2 diabetes among individuals suffering from OSA.

3.2 OBSTRUCTIVE SLEEP APNEA AND TYPE 1 DIABETES MELLITUS

While the major risk factor for OSA, obesity, is highly prevalent among individuals with type 2 diabetes, it is not uncommon to encounter high obesity rates among the type 1 diabetes population as well. For instance, in a well-established cohort of adult individuals with type 1 diabetes, the prevalence rates of overweight and obesity in the late 1980's were 28.6% and 3.4%, respectively [28]. After 18 years of follow-up these figures increased to 42% and 22.7%, respectively, at a higher rate than in the general population [28]. As the type 1 diabetes phenotype is changing, assessing the risk for OSA in this population is becoming more relevant. Furthermore, other factors associated with type 1 diabetes such as poor glycemic control and respiratory events during sleep relating to nocturnal hypoglycemia [18] (as later discussed) are also important for consideration while evaluating the risk of OSA in this population.

However, research studies among adults with type 1 diabetes are rare. Importantly, existing data on the prevalence of sleep apnea among individuals with this diabetes type, the majority of which conducted among youth/adolescents, are limited by the small number of individuals (7 to 50) evaluated [17-22].

4.0 METHODS

The purpose of this research was therefore to evaluate the prevalence of, as well as factors associated with, obstructive sleep apnea risk in a large cohort of long duration type 1 diabetes. We sought to identify the extent of the problem (i.e. sleep apnea) in this cohort as well as potentially modifiable risk factors associated with its presence. In addition, given prior publications suggesting gender differences in both the incidence of type 1 diabetes complications [29] as well as in risk factors associated with complication development [30-32], we further aimed to assess the potential role of gender in the presentation of sleep apnea risk.

This thesis specifically focused on addressing the following gaps in knowledge:

1) To determine the prevalence of sleep apnea risk among adults with long duration of type 1 diabetes and evaluate the presence of gender differences in its prevalence.

2) To identify risk factors associated with sleep apnea risk among adults with long duration of type 1 diabetes and evaluate the presence of differences in such factors by gender.

4.1 STUDY POPULATION

The study population comprised participants from the Pittsburgh Epidemiology of Diabetes Complications (EDC) study - an ongoing, 25-year prospective cohort of childhood-onset type 1 diabetes [33-34]. The EDC study was based on individuals diagnosed (or seen within one year of diagnosis) with incident childhood-onset (before age 17) type 1 diabetes at Children's Hospital of Pittsburgh between 1950 and 1980. Investigators recruited individuals residing within 100 miles

or two hours' drive from Pittsburgh, PA (n=658) and a first examination occurred between 1986 and 1988. This cohort has previously been shown to be representative of the type 1 diabetes population in Allegheny County, PA [35]. At baseline, the mean age of participants was 28 years, and their mean duration of diabetes was 20 years. Study participants were subsequently re-examined or surveyed every 2 years. The study protocol was approved by the University of Pittsburgh Institutional Review Board and all participants provided written informed consent prior to the initiation of any study procedure. Demographic, health care, diabetes self-care, and medical history information was obtained through self-administered questionnaires prior to each clinic visit.

During the 25-year examination that took place at the EDC clinic visit at the University of Pittsburgh between 2011 and 2014, a validated tool (as later discussed), the Berlin Questionnaire (BQ) [36], was introduced by a trained research assistant to the EDC participants for the first time to assess their risk of OSA. In addition to completing the questionnaire, individuals were also asked to report a history of diagnosed sleep apnea. A total of 170 out of 195 individuals who completed the questionnaire as of March 23rd, 2014 were included in this cross-sectional analysis.

4.2 THE BERLIN QUESTIONNAIRE

The BQ is a screening instrument used for classifying individuals as being at high or low risk for OSA through identifying their snoring behavior, daytime sleepiness, and history of obesity or hypertension. The questionnaire is divided into three categories concerned with 1) snoring (its loudness, frequency of occurrence, and whether it bothers other people) and cessation of breathing during sleep, 2) tiredness and fatigue, and 3) body mass index (BMI) and history of hypertension,

for a total of 10 questions. Individuals scoring positively on two or all of the three categories are considered to be at high risk for OSA. Those scoring positively on one or none of the categories are considered to be at low risk for OSA. The BQ questionnaire has been previously validated in a community survey and in a primary care setting against the sleep studies [36]. In primary care patients who were identified to be at high risk for OSA through a community survey (i.e. the BQ) and who then underwent sleep studies, the sensitivity and specificity were found to be 86% and 77%, respectively, while a positive predictive value and a likelihood ratio were 89% and 3.79, respectively [36]. The BQ was also previously validated in preoperative patients against different AHI scores obtained through in-laboratory polysomnography [37]. Obtained sensitivity, specificity, positive predictive value, and likelihood ratio at the AHI > 5 were 68.9%, 56.4%, 77.9%, and 1.58, respectively [37]. At the AHI >15, these figures changed to 78.6%, 50.5%, 50.9%, and 1.59, respectively [37]. This validation study demonstrated similar results for the STOP questionnaire (i.e. a validated screening tool for OSA in surgical patients) and for the American Society of Anesthesiologists' checklist for a routine screening of OSA in surgical patients.

Our study participants were classified as being at high risk for OSA if they scored positively on the BQ and/or self-reported a positive history of OSA diagnosis.

4.3 ANTHROPOMETRIC AND BLOOD PRESSURE MEASUREMENTS

Weight and percent body fat were obtained from a balance beam scale with participants wearing light clothing and no shoes. Height was obtained using a stadiometer. BMI was calculated as weight in kilograms (kg) divided by height in meters squared (m^2). Waist to hip ratio (WHR), a

measure of abdominal obesity, was calculated as the ratio of waist (measured at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the midaxillary line) to hip (measured at the widest point of the glutei, usually at the level of the greater femoral trochanter) girth. Waist to height ratio (WHTR), a measure of central obesity, was calculated as the ratio of waist to height. Blood pressure was measured with a random zero sphygmomanometer after a five-minute rest according to the Hypertension Detection and Follow-up Program Protocol [38]. The mean of the second and third readings was used. Hypertension (HTN) was defined as blood pressure ≥ 140/90 mm Hg or use of antihypertensive medications.

4.4 LABORATORY MEASUREMENTS

Fasting blood samples were taken. Blood glucose was obtained using the One Touch Ultra glucometer (LifeScan Inc., Milpitas, CA, USA). Hemoglobin A1c (HbA1c) was measured with the DCA 2000 Analyzer (Bayer, Tarrytown, NY, USA). Cholesterol and triglycerides were measured enzymatically by the Cholestech LDX System (Alere, Hayward, CA, USA), and high-density lipoprotein cholesterol (HDLc) after dextran sulphate precipitation. Low-density lipoprotein cholesterol (LDLc) was calculated using a previously validated [39] Friedewald equation [40]. Non-HDLc was calculated by subtracting HDLc from total cholesterol. To evaluate participants' insulin sensitivity, estimated glucose disposal rate (eGDR) was calculated using an equation derived from previous hyperinsulinemic euglycemic clamp studies (N=24) in which eGDR was highly related to glucose disposal during the clamp (r^2=0.63) [41]. The equation was: eGDR = 24.395 – (12.971*WHR) – (3.388*(HTN; "yes"=1, "no"=0)) – (0.601*(HbA1c – 1.13/0.81)).

4.5 DIABETES COMPLICATION ASSESSMENT

All diabetes complications were obtained from the last available EDC examination cycle (2008-2011). Coronary artery disease (CAD) presence was defined as by study-physician diagnosed angina, myocardial infarction confirmed by Q-waves on electrocardiogram (Minnesota codes 1.1 or 1.2) or hospital records, angiographic stenosis $\geq$50%, coronary artery bypass surgery, angioplasty, ischemic electrocardiogram changes (Minnesota codes 1.3, 4.1-4.3, 5.1-5.3, 7.1), or CAD death. The definition of hard CAD (hCAD) excluded angina and ischemic electrocardiogram changes. The presence of end-stage renal disease (ESRD) was established by a self-report of renal transplantation or renal dialysis.

4.6 OTHER COVARIATES

The following variables were also obtained from the last available EDC examination cycle (2008-2011). A history of severe hypoglycemia was defined as a hypoglycemic episode requiring external assistance (unconsciousness/seizure, required hospitalization, required help but did not recognize symptoms). History of stroke was determined through biennial surveys or physician interviews. When possible, medical or autopsy records were obtained to verify the occurrence and type of stroke. Confirmatory medical or autopsy records were obtained for 77% of the events. Stroke was defined as a neurological deficit of acute onset lasting $\geq$24 hours without other evident cause. Those participants who reported a history of smoking 100 or more cigarettes in their lifetime were considered past smokers.

4.7 STATISTICAL ANALYSIS

Quantile-quantile plots and histograms were used to check the distributions of each of the continuous variables for normality. Descriptive statistics were then performed, displaying means (standard deviations) or medians (interquartile range) for normally distributed and non-normally distributed variables, respectively. Participant characteristics overall and according to the gender for the relevant variables (BMI, percent body fat, WHR, WHTR, eGDR, and HDLc) were described using means, medians, or proportions as appropriate.

Univariate analyses were performed to describe the participants' prevalence of OSA risk and to compare their characteristics according to OSA status. Two-sided Student's *t* tests were used for normally distributed continuous variables, while two-sided nonparametric Wilcoxon's rank-sum tests were used for non-normally distributed continuous variables. Two-sided χ^2-tests or Fisher's exact tests, where appropriate, were used to assess differences in the distribution of categorical variables by OSA risk status. A p-value < 0.05 was considered statistically significant. Analyses were also repeated stratifying by gender.

Overall multivariable logistic regression was performed to assess independent correlates of the binary dependent variable of interest, OSA risk, and specifically, to assess whether lifestyle factors (i.e. obesity as measured by weight, BMI, percent body fat, waist and hip circumferences, WHR, and WHTR, systolic blood pressure (SBP), diastolic blood pressure (DBP), lipid profile, and smoking history), diabetes-related factors (i.e. fasting blood glucose, HbA1c, eGDR, HTN, and history of hypoglycemia that required assistance), and diabetes complications status (i.e. history of ESRD, CAD, hCAD, and stroke) differed among those individuals suffering from the outcome of interest and those with normal sleep patterns. Effect modification was assessed by testing plausible interaction terms (i.e. gender with BMI, HDLc, smoking history, and eGDR) at a

significance level of 0.10. Separate multivariable models were then built adjusting for gender and duration of diabetes and subsequently adding variables that were found to be statistically significant at an alpha level of 0.10 in the univariate analyses. Such variables were kept in the final regression model after ensuring that they were not collinear ($r < 0.6$).

Because the last category of the BQ is scored positively if an individual's BMI is greater than 30 kg/m^2 and/or if they report having high blood pressure, multivariable analyses were repeated in the same model-building fashion as previously described, only excluding those individuals with a BMI > 30 kg/m^2 and a positive HTN history. Due to the smaller sample size in these sub-analyses, a significance level of 0.10 was considered statistically significant.

Finally, gender multivariable sub-analyses (via model-building) were also performed at a significance level of 0.10, first, by not excluding those individuals who satisfied the last criteria of the BQ, second, by excluding individuals with a BMI > 30 kg/m^2, and third, by excluding the individuals with a BMI > 30 kg/m^2 and a positive HTN history.

All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

5.0 RESULTS

One hundred ninety-five out of 376 (51.9%) eligible participants completed the BQ up to March 23, 2014. A data freeze for this cross-sectional analysis occurred when 170 were entered (Figure 1).

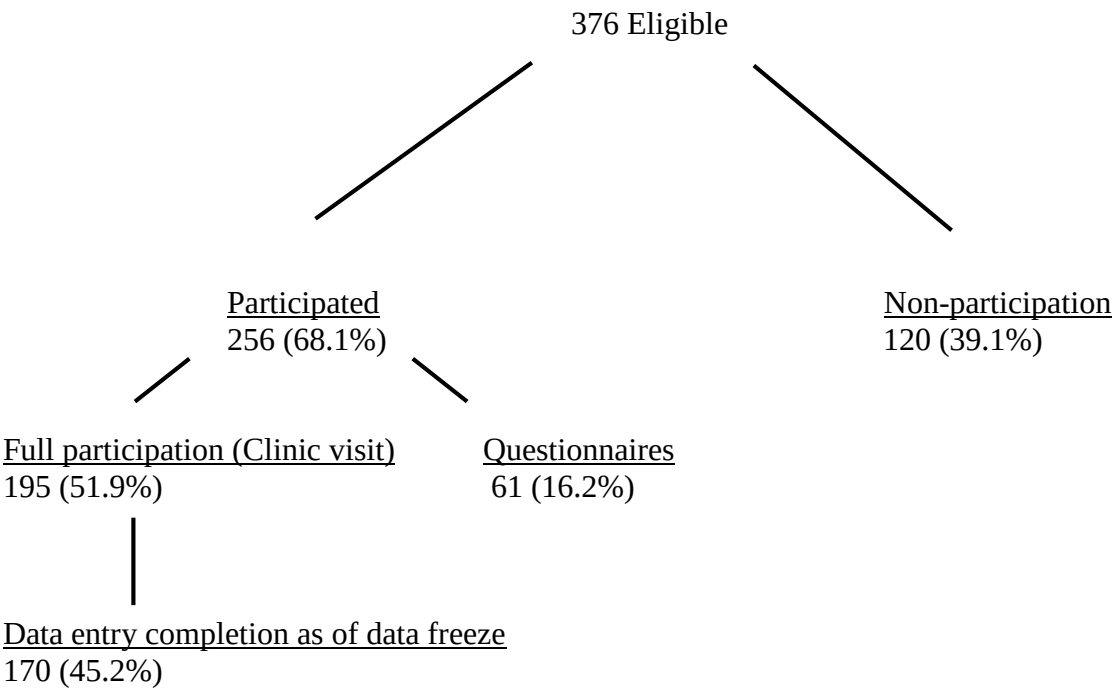

Figure 1. Epidemiology of Diabetes Complications Study 25-year follow-up participation tree

Table 1 shows the participants' overall characteristics. The mean participants' age was 51.4 ± 7.4 years and the median duration of diabetes was 42.3 (37.3, 46.6) years. About half (44.7%) were male. A self-reported history of diagnosed sleep apnea was present in 8.8% of the individuals. A little over a third of the participants (34.5%) reported having smoked at least 100 cigarettes in their lifetime. The participants were overweight with a median BMI of 26.8 (23.7, 30.9) kg/m^2.

Women were slightly more overweight than men. While both median systolic and average diastolic blood pressure were within a healthy range (<120/80 mm Hg), the prevalence of HTN among the participants was found to be 33.1% driven mainly by the one third of the participants (32.9%) taking antihypertensive medications. The overall median HbA1c was 7.6% (6.9%, 8.4%), indicating good glycemic control over the three months before the examined clinical visit. The participants' lipid profile was within normal limits. The overall insulin sensitivity, measured by the eGDR was 7.3 (5.7, 8.9) $mg*kg^{-1}*min^{-1}$, with women exhibiting higher insulin sensitivity than men (7.9 (6.2, 9.3) vs. 6.6 (4.6, 8.2) $mg*kg^{-1}*min^{-1}$, respectively). ESRD was reported among 8.8% of the participants, while CAD and hCAD history were present in 27.1% and 21.8% of the individuals, respectively. A low number of participants (3.5%) reported a positive stroke history, while 87.4% reported a history of hypoglycemia that required assistance.

Forty-four of the 170 participants (25.9% total prevalence; 25.0% males, 26.6% females) were at high OSA risk as per the BQ classification, in addition to a self-reported diagnosis of OSA. Of these 44 individuals, 15 had been previously diagnosed with OSA; five of these 15 individuals (33%) did not screen positively on the BQ. The OSA risk prevalence did not differ by gender (p-value=0.813).

Table 1. Characteristics of the EDC participants

Variable (unit)	N	Statistic*	
Age at exam (years)	170	51.4 ± 7.4	
Duration of diabetes (years)	170	42.3 (37.3, 46.6)	42.7 ± 6.6
Males (%)	76/170	44.7	
Self-reported OSA (%)	15/170	8.8	
Smoking history (%) $	165	34.5	
Height (cm)	170	167.4 ± 9.5	
Weight (kg)	170	78.0 ± 15.9	
BMI (kg/m^2)	170	26.8 (23.7, 30.9)	27.8 ± 5.3
Men	76	26.5 (23.7, 30.5)	27.3 ± 4.5
Women	94	27.4 (23.4, 31.9)	28.4 ± 5.9
Body fat (%)	135	28.5 (20.0, 38.6)	29.7 ± 12.7
Men	64	20.0 (15.5, 26.0)	21.3 ± 8.0
Women	71	36.9 (28.8, 44.8)	37.3 ± 11.4
Waist circumference (cm)	167	90.8 (80.7, 101.9)	92.0 ± 14.1
Hip circumference (cm)	167	104.4 (98.0, 111.6)	105.5 ± 11.0
Waist to hip ratio	166	0.87 (0.81, 0.93)	0.87 ± 0.09
Men	74	0.92 (0.86, 0.98)	0.92 ± 0.07
Women	92	0.83 (0.77, 0.88)	0.83 ± 0.08
Waist to height ratio	166	0.54 (0.48, 0.60)	0.55 ± 0.09
Men	74	0.53 (0.49, 0.60)	0.55 ± 0.07
Women	92	0.55 (0.47, 0.60)	0.55 ± 0.10
Hemoglobin A1c (%)	170	7.6 (6.9, 8.4)	7.7 ± 1.3
Fasting blood glucose (mg/dL)	165	158.0 (115.0, 204.0)	168.2 ± 74.8
eGDR ($mg*kg^{-1}*min^{-1}$) $	165	7.3 (5.7, 8.9)	7.1 ± 2.3
Men	73	6.6 (4.6, 8.2)	6.3 ± 2.4
Women	92	7.9 (6.2, 9.3)	7.8 ± 2.1
SBP (mmHg)	168	115.0 (106.5, 122.5)	117.1 ± 20.8
DBP (mmHg)	167	65.7 ± 9.0	
HTN (%)	56/169	33.1	
HTN medicine use ** (%)	47/143	32.9	
Pulse (beats/min)	169	74.0 (66.0, 80.0)	73.0 ± 10.4
Total cholesterol (mg/dL)	170	178.0 (153.0, 196.0)	176.2 ± 37.4
LDLc (mg/dL)	147	99.5 ± 30.4	
HDLc (mg/dL)	170	58.0 (47.0, 73.0)	60.4 ± 19.0
Men	76	48.0 (41.5, 59.5)	51.3 ± 15.5
Women	94	67.8 ± 18.4	
Non-HDLc (mg/dL)	168	110.5 (95.0, 139.0)	117.0 ± 35.9
Total triglycerides (mg/dL)	169	69.0 (49.0, 96.0)	89.2 ± 65.9
End-stage renal disease (%) $	15/170	8.8	
CAD history (%) $	46/170	27.1	
Hard CAD history (%) $	37/170	21.8	
Stroke history (%) $	6/170	3.5	
Hypoglycemia (%) *** $	125/143	87.4	

*Values are either mean ± SD, median (25^{th} %, 75^{th} %) or sample size (%)

** 27 missing values due to the data freeze for this analysis

*** History of hypoglycemia that required assistance

$ Variables obtained from the last available EDC examination cycle (2008-2011)

Univariately (Table 2), individuals at a high risk for OSA had a borderline longer duration of diabetes (p=0.089), were heavier (p=0.024), had a higher BMI (p=0.002), waist and hip circumferences (p=0.013, p=0.023, respectively), WHTR (p=0.009), SBP (p=0.033), and total triglycerides (p=0.005), as well as lower HDLc (p=0.045), and borderline lower eGDR (0.090); they were also more likely to report a positive history of smoking (p=0.091). The two groups did not significantly differ with respect to age, gender, HbA1c, fasting blood glucose, DBP, total and LDLc concentration, and history of HTN, ESRD, CAD, hCAD, stroke, and hypoglycemia that required assistance.

The results from univariate analyses stratified by gender are displayed in Tables 3 and 4. Females at a high risk for OSA were on average heavier (p=0.020), had a higher BMI (p=0.003), waist and hip circumferences (p=0.023, p=0.040, respectively), WHTR (p=0.013), and total triglycerides (p=0.048), and a borderline higher WHR (p=0.054). They also reported a higher use of antihypertensive medications (p=0.037), and were more likely to have been diagnosed with CAD or hCAD (p=0.083 and p=0.065, respectively). In addition, high-risk OSA females had a lower HDLc concentration as well as eGDR (p=0.009 and p=0.037, respectively). The two groups of women did not significantly differ with respect to age, duration of diabetes, HbA1c, fasting blood glucose, systolic and diastolic blood pressure, total and LDLc levels, or in terms of a history of smoking, HTN, ESRD, stroke, and hypoglycemia that required assistance.

Men with type 1 diabetes at high risk for OSA exhibited higher DBP (p=0.040), total cholesterol (p=0.034) and triglyceride concentrations (p=0.065), and were more likely to have reported a positive history of smoking (p=0.025) (Table 4). The two OSA groups of men did not significantly differ with respect to the rest of the demographic, clinical, or diabetes complications variables.

Table 2. Participants' characteristics by OSA risk status*

Variable (unit)	N	OSA low risk	N	OSA high risk	p-value
Age at exam (years)	126	51.1 ± 7.3	44	52.1 ± 7.7	0.4499
Males (%)	57	45.2	19	43.2	0.8133
Duration of diabetes (years)	126	41.8 (36.4, 46.4), 42.2 ± 6.5	44	43.5 (39.3, 49.2), 44.1 ± 6.6	0.0887
Smoking history (%) $	38	30.9	19	45.2	0.0914
Height (cm)	126	167.8 ± 9.5	44	166.4 ± 9.6	0.4099
Weight (kg)	126	76.1 ± 14.3	44	83.3 ± 18.9	**0.0241**
BMI (kg/m^2)	126	26.4 (23.5, 30.0), 27.0 ± 30.1	44	29.6 (24.3, 36.1), 30.1 ± 6.5	**0.0024**
Body fat (%)	101	28.6 (20.1, 38.0), 29.3 ± 31.1	34	28.4 (18.8, 42.2), 31.1±15.5	0.8235
Waist circumference (cm)	124	90.6 (80.3, 96.7), 90.0 ± 12.2	42	98.4 (81.4, 111.8), 97.7 ± 17.6	**0.0130**
Hip circumference (cm)	124	103.3 (97.9, 109.7), 104.2 ± 9.4	42	108.7 (98.2, 119.2) 109.5 ± 14.3	**0.0232**
Waist to hip ratio	124	0.86 (0.81, 0.93), 0.86 ± 0.09	42	0.89 (0.82, 0.94), 0.89 ±0.09	0.1511
Waist to height ratio	124	0.52 (0.48, 0.58), 0.54 ± 0.07	42	0.60 (0.50, 0.66), 0.59 ±0.11	**0.0094**
Hemoglobin A1c (%)	126	7.6 (6.9, 8.4), 7.7 ± 1.3	44	7.5 (6.8, 8.4), 7.7 ± 1.3	0.9008
Fasting blood glucose (mg/dL)	124	160.5 (115.0, 203.5), 167.3 ± 69.2	41	148.0 (101.0, 210.0), 170.7 ± 90.5	0.6949
eGDR ($mg*kg^{-1}*min^{-1}$) $	123	7.7 (5.8, 9.1), 7.2 ± 2.3	42	6.7 (5.3, 8.4), 6.6 ± 2.4	0.0898
SBP (mmHg)	124	115.0 (105.0, 121.0), 115.9 ± 21.4	44	117.5 (108.0, 129.0) 120.5 ± 18.8	**0.0328**
DBP (mmHg)	123	65.1 ± 8.8	44	67.4 ± 9.6	0.1608
HTN (%)	39	31.2	17	38.6	0.3674
HTN medicine use (%)	33	30.3	14	41.2	0.2374
Pulse (beats/min)	126	74.0 (66.0, 80.0), 73.2 ± 10.6	43	72.0 (64.0, 80.0), 72.6± 10.1	0.8379
Total cholesterol (mg/dL)	126	175.0 (149.0, 196.0), 175.0 ± 38.3	44	182.5 (160.5, 199.5), 179.7 ± 34.9	0.1541
LDLc (mg/dL)	107	98.6 ± 30.3	40	101.9 ± 31.0	0.5634
HDLc (mg/dL)	126	60.0 (48.0, 75.0), 62.2 ± 19.0	44	50.5 (41.0, 71.5), 55.5± 18.4	**0.0455**
Non-HDLc (mg/dL)	124	108.0 (92.5, 136.0), 114.5 ± 34.9	44	122.0 (102.0, 145.0) 124.3 ± 38.1	0.1007
Total triglycerides (mg/dL)	126	64.5 (44.0, 87.0), 82.6 ± 56.8	43	78.0 (58.0, 126.0), 108.5 ± 85.1	**0.0048** 0.2196
End-stage renal disease (%) $	9	7.1	6	13.6	
CAD history (%) $	31	24.6	15	34.1	0.2226
Hard CAD history (%) $	24	19.0	13	29.5	0.1463
Stroke history (%) $	4	3.2	2	4.5	0.6496
Hypoglycemia (%) ** $	93	85.3	32	94.1	0.2422

* Values are either means ± SD, medians (25^{th} %, 75^{th} %) or sample size (%)

** History of hypoglycemia that required assistance

$ Variables obtained from the last available EDC examination cycle (2008-2011)

Table 3. Participants' characteristics by OSA risk status, women*

Variable (unit)	N	OSA low risk	N	OSA high risk	p-value
Age at exam (years)	69	51.5 ± 7.2	25	52.4 ± 6.9	0.6082
Duration of diabetes (years)	69	42.3 (36.6, 46.4), 42.4 ± 6.8	25	43.2 (39.3, 48.0), 43.9 ± 6.5	0.3167
Smoking history (%) $	23	34.3	9	37.5	0.7801
Height (cm)	69	162.1 ± 6.4	25	160.4 ± 7.3	0.2852
Weight (kg)	69	71.0 ± 12.6	25	81.5 ± 20.1	**0.0204**
BMI (kg/m^2)	69	26.5 (23.3, 30.0), 27.0 ± 4.9	25	32.5 (26.0, 36.9), 31.5 ± 7.1	**0.0030**
Body fat (%)	55	35.6 (28.8, 42.4), 36.5 ± 9.2	16	44.0 (27.6, 51.6), 40.0 ±16.9	0.2739
Waist circumference (cm)	68	86.1 (77.0, 92.5), 86.6 ± 11.5	24	97.0 (79.8, 114.1), 97.0 ± 19.4	**0.0228**
Hip circumference (cm)	68	105.8 ± 10.1	24	113.5 ± 16.5	**0.0405**
Waist to hip ratio	68	0.82 (0.75, 0.87), 0.82 ±0.08	24	0.86 (0.80, 0.90), 0.85 ±0.08	**0.0542**
Waist to height ratio	68	0.53 (0.47, 0.58), 0.53 ±0.08	24	0.62 (0.49, 0.68), 0.60 ±0.12	**0.0126**
Hemoglobin A1c (%)	69	7.7 ± 1.1	25	7.7 ± 1.2	0.8012
Fasting blood glucose (mg/dL)	68	169.5 (115.0, 211.5), 169.5 ± 69.4	22	147.5 (116.0, 210.0), 170.0 ± 84.1	0.7283
eGDR ($mg*kg^{-1}*min^{-1}$) $	68	8.6 (7.0, 9.5), 8.0 ± 2.0	24	6.8 (5.5, 8.5), 7.1 ± 2.2	**0.0363**
SBP (mmHg)	69	115.0 (105.0, 121.0), 114.7 ± 17.1	25	116.0 (108.0, 127.0), 117.4 ± 14.8	0.2711
DBP (mmHg)	69	63.7 ± 8.8	25	64.0 ± 9.5	0.8893
HTN (%)	19	27.5	10	40.0	0.2477
HTN medicine use (%)	15	25.0	10	50.0	**0.0367**
Pulse (beats/min)	69	73.0 ± 8.6	25	72.4 ± 8.4	0.7536
Total cholesterol (mg/dL)	69	180.4 ± 33.9	25	180.4 ± 35.5	0.9926
LDLc (mg/dL)	61	96.5 ± 28.2	23	99.0 ± 33.3	0.7275
HDLc (mg/dL)	69	70.8 ± 16.8	25	59.6 ± 20.4	**0.0085**
Non-HDLc (mg/dL)	67	106.0 (91.0, 134.0), 112.5 ± 32.7	25	108.0 (99.0, 139.0), 121.0 ± 39.4	0.4476
Total triglycerides (mg/dL)	69	64.0 (48.0, 80.0), 74.5 ± 45.1	24	75.0 (56.5, 116.0), 97.2 ± 58.5	**0.0481**
End-stage renal disease (%) $	4	5.8	3	12.0	0.3778
CAD history (%) $	13	18.8	9	36.0	0.0825
Hard CAD history (%) $	9	13.0	8	32.0	0.0647
Stroke history (%) $	3	4.3	1	4.0	1.0000
Hypoglycemia (%) ** $	52	86.7	19	95.0	0.4375

* Values are either means ± SD, medians (25^{th} %, 75^{th} %) or sample size (%)

** History of hypoglycemia that required assistance

$ Variables obtained from the last available EDC examination cycle (2008-2011)

Table 4. Participants' characteristics by OSA risk status, men*

Variable (unit)	N	OSA low risk	N	OSA high risk	p-value
Age at exam (years)	57	50.6 ± 7.3	19	51.7 ± 8.9	0.5945
Duration of diabetes (years)	57	41.7 (36.1, 46.3), 41.8 ± 6.1	19	43.5 (40.2, 49.2), 44.4 ± 7.0	0.1677
Smoking history (%) $	15	26.8	10	55.6	**0.0248**
Height (cm)	57	174.7 ± 8.0	19	174.3 ± 6.0	0.8401
Weight (kg)	57	82.4 ± 13.7	19	85.8 ± 17.4	0.3823
BMI (kg/m^2)	57	26.2 (23.8, 30.0), 27.0 ± 4.3	19	28.7 (23.4, 31.9), 28.2 ± 5.2	0.4285
Body fat (%)	46	19.3 (15.3, 23.8), 20.6 ± 7.8	18	21.5 (17.5, 28.5), 23.1 ± 8.5	0.3135
Waist circumference (cm)	56	91.5 (85.6, 103.3), 94.2 ± 11.8	18	98.6 (87.2, 111.0), 98.5 ± 91.0	0.2870
Hip circumference (cm)	56	102.3 ± 8.2	18	104.2 ± 8.4	0.3941
Waist to hip ratio	56	0.92 (0.86, 0.97), 0.92± 0.06	18	0.94 (0.86, 1.02), 0.95 ± 0.09	0.3351
Waist to height ratio	56	0.52 (0.49, 0.59), 0.54± 0.07	18	0.56 (0.50, 0.63), 0.56 ± 0.08	0.2986
Hemoglobin A1c (%)	57	7.7 (6.8, 8.4), 7.8 ± 1.6	19	7.7 (6.8, 8.4), 7.8 ± 1.5	0.9426
Fasting blood glucose (mg/dL)	56	158.0 (115.5, 191.5), 164.7 ± 69.6	19	171.0 (94.0, 218.0), 171.6 ± 99.8	0.8550
eGDR ($mg*kg^{-1}*min^{-1}$) $	55	6.6 (4.6, 8.2), 6.3 ± 2.4	18	6.4 (4.3, 8.4), 6.1 ± 2.6	0.7734
SBP (mmHg)	55	114.0 (106.0, 121.0), 117.5 ± 25.8	19	118.0 (113.0, 133.0), 124.6 ± 22.9	0.1188
DBP (mmHg)	54	68.5 (59.0, 75.0), 67.0 ± 8.5	19	74.0 (66.0, 77.0), 71.9 ± 7.8	**0.0396**
HTN (%)	20	35.7	7	36.8	0.9295
HTN medicine use (%)	18	36.7	4	28.6	0.7532
Pulse (beats/min)	57	73.3 ± 12.7	18	73.0 ± 12.3	0.9183
Total cholesterol (mg/dL)	57	170.0 (141.0, 182.0), 168.5 ± 42.4	19	183.0 (174.0, 198.0), 178.8 ± 35.1	**0.0342**
LDLc (mg/dL)	46	101.4 ± 33.0	17	105.8 ± 28.2	0.6335
HDLc (mg/dL)	57	48.0 (43.0, 57.0), 51.7 ±16.0	19	47.0 (36.0, 62.0), 50.1 ± 14.1	0.6965
Non-HDLc (mg/dL)	57	115.0 (95.0, 139.0), 116.8 ± 37.5	19	131.0 (107.0, 146.0), 128.6 ± 36.8	0.1231
Total triglycerides (mg/dL)	57	65.0 (44.0, 108.0), 92.3 ± 67.5	19	92.0 (69.0, 130.0), 122.7 ± 110.2	0.0655
End-stage renal disease (%) $	5	8.8	3	15.8	0.4045
CAD history (%) $	18	31.6	6	31.6	1.0000
Hard CAD history (%) $	15	26.3	5	26.3	1.0000
Stroke history (%) $	1	1.8	1	5.3	0.4400
Hypoglycemia (%) ** $	41	83.7	13	92.9	0.6697

* Values are either means ± SD, medians (25^{th} %, 75^{th} %) or sample size (%)

** History of hypoglycemia that required assistance

$ Variables obtained from the last available EDC examination cycle (2008-2011)

The presence of effect modification was assessed prior to constructing full multivariable models. No statistically significant interaction terms were observed between gender and any of the following variables: BMI, HDLc, smoking history, or eGDR (p=0.281, p=0.205, p=0.145 and

p=0.365, respectively). In the overall logistic regression analyses, all previously mentioned univariately significant variables at a p-value of 0.10 were subsequently individually added to a regression model along with duration of diabetes and gender. A total of nine models were thus built. Variables with a p-value < 0.10 comprised the final model. Weight (p=0.003), BMI (p=0.002), waist and hip circumferences (p=0.003 and p=0.009, respectively), WHTR (p=0.004), HDLc (p=0.014), and triglyceride levels (p=0.029) remained statistically significant after adjustment for diabetes duration and gender, smoking history remained borderline significant (p=0.097), and SBP lost its significance (p=0.385). Before arriving to the final regression model, each of the eight statistically significant variables were checked for multicollinearity. Because BMI was the most statistically significant variable in the model building process and was highly correlated with weight (r=0.824, p<0.0001), waist circumference (r=0.853, p<0.0001), hip circumference (r=0.885, p<0.0001), and WHTR (r=0.901, p<0.0001), it was the only variable out of the four that was chosen to stay in the final model. Therefore, in addition to BMI, the final model comprised duration of diabetes, gender, HDLc, triglycerides, and smoking history. Given that triglycerides lost statistical significance after controlling for the above mentioned variables (odds ratio (OR) 1.003 (95% confidence interval (CI) = 0.997, 1.009, p=0.375)), it was excluded from the final model. Therefore, BMI (directly), smoking history (inversely), and HDLc (inversely), emerged as correlates of OSA risk in the final logistic regression model (Table 5). Duration of diabetes remained a borderline positive correlate of OSA risk. While gender did not show statistical significance, it was “forced” to remain in the final model. BMI and smoking history were significantly positively associated with OSA status (OR 1.097 (95% CI=1.023, 1.177, p=0.010) and OR 2.266 (95% CI=1.046, 4.912, p=0.038), respectively), while HDLc showed a negative significant association (OR 0.974 (95% CI=0.950, 0.997, p=0.030).

Table 5. Final logistic regression model, overall analysis

N=165; 42 (25.4%) events

Variables selected in the final model	OR	95% CI	P-value
Gender	1.560	0.659, 3.691	0.3114
Diabetes duration	1.049	0.991, 1.111	0.0999
BMI	1.097	1.023, 1.177	0.0095
Smoking history $	2.266	1.046, 4.912	0.0381
HDLc	0.974	0.950, 0.997	0.0301

$ Variable obtained from the last available EDC examination cycle (2008-2011)

Sub-analyses were performed, excluding individuals with a BMI greater than 30 kg/m^2 as well as those with a positive history of HTN, as those criteria were part of the BQ-determined OSA definition. However, adjusting for the duration of diabetes and gender, no further variables significantly contributed to the logistic regression model.

Table 6 displays the overall final logistic regression model for female participants. This model was arrived to in the same manner as for the overall analyses. After controlling for duration of diabetes in the model-building process, along with all of the previously described univariately significant gender-specific variables, BMI (directly) and HDLc (inversely) emerged as OSA risk correlates in the final model. While, BMI was significantly positively associated with the outcome (OR 1.126 (95% CI=1.033, 1.226, p=0.007)), HDLc was significantly negatively associated with it (OR 0.968 (95% CI=0.940, 0.997, p=0.031)).

Table 6. Final logistic regression model, women

N=94; 25 (26.6%) events

Variables selected in the final model	OR	95% CI	P-value
Diabetes duration	1.046	0.971, 1.127	0.2390
BMI	1.126	1.033, 1.226	0.0068
HDLc	0.968	0.940, 0.997	0.0315

Further restricting multivariable analyses among women to those with a BMI $\leq$ 30 kg/m^2 (Table 7), BMI lost its statistical significance, while HDLc and hCAD emerged as correlates of OSA risk in the final model (OR 0.966 (95% CI=0.927, 1.006, p=0.096) and OR 6.817 (95%CI=1.214, 38.276, p=0.029), respectively). After further exclusion of women with a positive HTN history (Table 8), HDLc emerged as the only statistically significant variable while controlling for duration of diabetes (OR 0.948 (95% CI=0.899, 1.001, p=0.053)).

Table 7. Final logistic regression model, women with a BMI ≤ 30 kg/m2

N=62; 11 (17.7%) events

Variables selected in the final model	OR	95% CI	P-value
Diabetes duration	1.001	0.892, 1.124	0.9823
HDLc	0.966	0.927, 1.006	0.0956
Hard CAD $	6.817	1.214, 38.276	0.0292

$ Variable obtained from the last available EDC examination cycle (2008-2011)

Table 8. Final logistic regression model, women with a BMI ≤ 30 kg/m2 and no HTN

N=46; 7 (15.2%) events

Variables selected in the final model	OR	95% CI	P-value
Diabetes duration	0.970	0.837, 1.124	0.6814
HDLc	0.948	0.899, 1.001	0.0534

Lastly, among men, controlling for duration of diabetes and subsequently adding each of the univariately significant gender-specific variables (DBP, total cholesterol, triglycerides, and smoking history) to the multivariable models, DBP (OR 1.115 (95% CI=1.024, 1.214, p=0.012)), and smoking history (OR 3.666 (95% CI=1.075, 12.505, p=0.038)) emerged as the positive OSA risk correlates in the final model (Table 9).

Table 9. Final logistic regression model, men

N=71; 18 (25.3%) events

Variables selected in the final model	OR	95% CI	P-value
Diabetes duration	1.100	0.991, 1.221	0.0748
DBP	1.115	1.024, 1.214	0.0122
Smoking history $	3.666	1.075, 12.505	0.0380

$ Variable obtained from the last available EDC examination cycle (2008-2011)

Restricting the analyses to men with a BMI ≤ 30 kg/m^2, DBP remained directly associated with the outcome (OR 1.124 (95% CI=1.019, 1.241, p=0.020), Table 10). However, in the final

model restricted to the male individuals with a BMI ≤ 30 kg/m^2 and no HTN, DBP expectedly lost its statistical significance and no other variables significantly contributed to the model.

Table 10. Final logistic regression model, men with a BMI ≤ 30 kg/m2

N=51; 12 (23.5%) events

Variables selected in the final model	OR	95% CI	P-value
Diabetes duration	1.162	1.012, 1.334	0.0334
DBP	1.124	1.019, 1.241	0.0200

6.0 DISCUSSION

6.1 SUMMARY OF FINDINGS AND DISCUSSION OF LITERATURE

In this cross-sectional analysis of 170 men and women in their early 50's, with long-standing type 1 diabetes, attending the 25-year examination of the Pittsburgh EDC study, we found that approximately one fourth were at a high risk for OSA regardless of gender. Three modifiable risk factors, BMI, smoking history, and HDLc concentration, were associated with a high risk for OSA after taking the participants' duration of diabetes and gender into account. However, after excluding those individuals with a BMI greater than 30 kg/m^2 and a positive history of HTN, the relationships between the previously mentioned modifiable risk factors and OSA status attenuated and none remained statistically significant. While the prevalence of high OSA risk did not significantly differ with respect to the participants' gender, men and women exhibited different risk profiles for OSA. While BMI and HDLc were strongly associated with sleep apnea risk status in women and hCAD history was strongly correlated with OSA risk status in non-obese women, DBP and smoking history were isolated as correlates of high sleep apnea risk in men after accounting for the participants' diabetes duration. In the more restrictive gender-specific sub-analyses from which women and men with a BMI greater than 30 kg/m^2 and a positive history of HTN were excluded, HDLc was still significantly inversely related to OSA risk status in women, while BMI became statistically insignificant. Similarly, the strong relationships between DBP and smoking history with the presence of high OSA risk became insignificant after the same restrictions were applied to men.

The OSA risk prevalence in this cohort of adults with long duration type 1 diabetes appears similar to the previously reported OSA prevalence in the general population [8]. Specifically, Heistand et al. (2006) examined the prevalence of OSA, as determined by the BQ scores, among 1,506 nationally-representative adults (mean age 49 years) who completed the National Sleep Foundation's *Sleep in America* 2005 Poll and found that 31% of men fell in the high-risk category compared to only 21% of women ($p<0.001$) [8]. However, in this study of individuals with type 1 diabetes, we did not observe differences in OSA risk prevalence by gender. To our knowledge, to the present date there has only been one other study that has examined the prevalence of and risk factors associated with OSA risk (as determined by the BQ) in a sample of adults with long standing type 1 diabetes (N=99, 55.5% men, mean age 43.9 ± 1.3 years, mean duration of diabetes 26.9 ± 1.3 years, mean BMI 24.5 ± 0.3 kg/m^2, and mean HbA1c 7.8 ± 0.1 %) [42]. Compared to our study, van Dijk et al. (2011) found a slightly lower prevalence of high OSA risk (17.2%) [42]. However, our definition of OSA also included a diagnosis of self-reported sleep apnea. Nevertheless, even after excluding those individuals with an OSA diagnosis from the analysis, the total prevalence of high OSA risk in our study was still slightly higher (22.5 % total population, 24.7% women, 19.7% men, p-value for a gender difference, 0.439) than in the previously mentioned study. Gender differences with respect to OSA risk status were not examined in the above mentioned study. It could be speculated, however, that the lower prevalence of OSA risk in the study by van Dijk et al. (2011) was likely a result of a younger population with a shorter duration of diabetes and a lower BMI.

Fifteen out of 170 (8.8%) participants reported a previous diagnosis of sleep apnea, which is very comparable to self-reported rates (9%) of diagnosed sleep apnea in the U.S. [6]. Five of these participants did not score positively on the BQ, most likely due to active OSA treatment (via

continuous positive air pressure therapy (CPAP) during sleep). Though polysomnography would be required to objectively confirm the BQ-defined rates of OSA, these figures suggest that 29 out of 44 (65.9%) individuals who were determined to be at a high risk for OSA via the BQ remained undiagnosed, despite having a chronic condition such as type 1 diabetes, which requires frequent medical visits. In the general population, it has been reported that approximately 75-80% of individuals with OSA are undiagnosed [7]. Moreover, given that not all eligible study participants were able to attend the 25th-year clinical examination (during which the BQ was administered), the most frequent reason being related to complications associated with their type 1 diabetes, the true prevalence of OSA risk in our study population is likely higher than reported here.

Previous studies that examined a relationship between sleep disorders and diabetes have mainly focused on adults with type 2 diabetes mellitus [9-15]. Although there have been studies that assessed such a relationship among individuals suffering from type 1 diabetes, most were limited to youth [17-18, 20-21] and small samples [17-22]. For instance, Villa et al. (2000) examined 25 children with type 1 diabetes (mean age 7.7 ± 2.0 years, mean duration of diabetes 2.7 ± 2.6 years, mean BMI 18.7 ± 3.6 kg/m^2, and mean HbA1c 7.8 ± 1.1 %) and 20 healthy controls of similar age and BMI after an overnight polysomnography and found that more cases than controls had sleep apneas ($p= 0.006$) and that they lasted longer ($p= 0.07$) [18]. In addition, patients with poorly controlled diabetes (HbA1c ≥ 8.0%) exhibited more apneas compared to patients with well controlled diabetes (HbA1c ≤ 7.9%) and to controls ($p< 0.0001$). Glycemic control and duration of diabetes correlated significantly with the respiratory events during sleep in the children with type 1 diabetes ($r= 0.36$, $p=0.09$, and $r= 0.43$, $p= 0.04$, respectively) [18]. Interestingly, in this study, we did not observe a significant relationship between glycemic control and OSA risk status in adults, as also previously reported among adult individuals with type 1 diabetes [42]. While this

finding may show that children and adults exhibit different risk factors associated with OSA, it is also possible that disturbed sleep patterns may still impair glucose metabolism in adults suffering from type 1 diabetes, but that this mechanism may not solely be reflected in the HbA1c values (although the participants from the abovementioned study [18], in which a significant relationship between sleep apneas and glycemic control was observed, had equally low HbA1c values as our participants). Other factors related to glycemic control/insulin sensitivity, such as obesity, lipid concentrations, and eGDR, may instead become more important in adulthood and play a greater role in the development of OSA. Specifically, our study found that BMI and HDLc concentration were independently associated with OSA risk status, while univariately, eGDR was significantly related to OSA risk in the overall EDC cohort and among women.

A number of diabetes-related factors could be associated with disturbed sleep patterns, including modifiable lifestyle factors such as obesity, the aforementioned glycemic control, as well as diabetes-associated complications, such as CAD. Our study found that modifiable lifestyle factors including BMI, DBP, HDLc, and history of smoking, as well as unmodifiable disease states, e.g. hCAD history, were independently associated with OSA risk status. Previous studies have well established that obesity (measured by several markers including BMI, WHR, and neck circumference) is the strongest risk factor for OSA [25, 43-46] and that more than half of the prevalence of OSA can be attributed to excess body weight [43, 46]. Our study confirmed this finding as BMI was found to be the strongest independent correlate of OSA risk status. Moreover, when analyses were restricted to non-obese individuals (BMI less than 30 kg/m^2) the associations with other OSA correlates attenuated. As obesity is highly associated with lipid concentrations [47], in particular, inversely with HDLc, it is not unexpected that we also found an association between OSA risk status and HDLc. However, previous studies that examined the relationship

between OSA and type 1 diabetes-related factors in adults did not focus on studying the association between OSA and lipid concentrations [42, 48].

A potential pathophysiological association between OSA and obesity includes elevation of the “hunger hormone,” ghrelin, and resistance of the “satiety hormone,” leptin, as a result of sleep restriction, which contributes to obesity and, therefore, to insulin resistance [16]. During the insulin-resistant state, the counterregulatory hormones, glucagon, catecholamines, and cortisol, then increase blood glucose [16]. In addition, during the sleep-restricted state, growth hormone does not compete against catecholamines, which then further contributes to increasing blood glucose [16]. Sleep arousals also cause cortisol and catecholamines to elevate, and therefore, increase blood glucose [16]. In addition, hypoxia and interrupted sleep contribute to the release of cytokines, namely tumor necrosis factor alpha and interlukin-6, which are also linked to insulin resistance and diabetes [16]. Although, the present study was not designed to distinguish the mechanism of this cycle between OSA, obesity, and insulin resistance, the strong independent association between OSA risk status and obesity that we observed confirms the well-established link between the two conditions.

Young et al. (2004) suggested that smoking also is a possible risk factor for OSA, though few studies were conducted to examine such a relationship [7]. They proposed that airway inflammation and smoking-associated disease may play a role in a relationship between smoking and OSA [7]. While our study found that past smoking history was independently associated with OSA risk, especially in men, the Wisconsin Sleep Cohort study [49] reported that current smokers were three times more likely to have OSA than former or never smokers and suggested that the effect of smoking on OSA is reversible after smoking cessation. Unfortunately, as of the writing

of this thesis, collected data on the EDC participants' current smoking status were unavailable for the evaluation of its association with OSA status.

HTN is another well-established risk factor associated with OSA [7]. While our study did not show that HTN history was independently associated with OSA risk status, DBP was found to be directly associated with the outcome in men. Schober et al. (2011) evaluated the prevalence of and risk factors associated with sleep disturbed patterns among adults with both type 1 and type 2 diabetes (N=58 and 498, respectively) by assessing their airflow and pulse oximetry through a screening device named ApneaLink Oxi [48]. They also found a higher prevalence of hypertension, along with cardiovascular disease, heart failure, neuropathy, and nephropathy in a group of participants with moderate to severe OSA (AHI $\geq$ 15/hour). While an association between ESRD and OSA status was not seen in our study and we did not evaluate neuropathy and heart failure, we did find that non-obese women with a positive history of hard CAD had 6.8 times higher odds (p= 0.029) of being at high risk for OSA compared to non-obese women without a hard CAD event, after taking into account their diabetes duration and HDLc levels. Because both our study and the above-mentioned study were of cross-sectional nature, it is impossible to evaluate whether cardiovascular disease occurred before or after the individuals became at high OSA risk. However, while one previous prospective study (N=308, seven years of follow-up) found OSA to be an independent significant predictor of incident CAD (relative risk 4.6, 95% CI=1.83, 11.6, p= 0.001) [50], the same observational study also found that participants with prevalent OSA had an increased risk of developing CAD compared to those who snored but did not have OSA (16.2 % vs 5.4%, p= 0.003). Fortunately, another prospective study found a benefit of OSA treatment in reducing new cardiovascular events in CAD patients [51].

6.2 STUDY STRENGTHS AND LIMITATIONS

To our knowledge, this is one of the first studies that evaluated the prevalence of and risk factors associated with OSA risk through a screening instrument in a well-phenotyped, relatively large adult population with long duration type 1 diabetes mellitus. In addition, to our knowledge our study was also the first to explore gender-specific risk factors associated with OSA risk status as determined by the Berlin Questionnaire. However, there are also certain limitations to the present study. Primarily, due to the cross-sectional nature of our analyses, it is impossible to establish temporality between OSA risk status and type 1 diabetes-related factors. Precaution should therefore be taken when interpreting the results of our study as they should be validated against future prospective data. Furthermore, given that our study population has survived type 1 diabetes for over 40 years, considerable survival bias is present in the current study. This type of bias may have resulted in an underestimation of the estimated prevalence of OSA risk, especially as the time during which the EDC population has been followed has been marked with increasing prevalence of the OSA's major risk factor, obesity. As previously discussed, Conway et al. (2010) have confirmed the increasing prevalence of overweight and obesity in the type 1 diabetes cohort as well [28]. Lastly, because not all of the BQ data were available for timely analyses of this thesis, other potential correlates of OSA risk could have been overlooked or underestimated due to the limited size of the current sample.

6.3 FUTURE DIRECTIONS

Upon availability of the rest of the BQ data, along with the diabetes complications data from the current EDC examination cycle, the present analyses will be repeated with the aim of re-evaluating the prevalence and correlates of OSA risk in a larger sample. In addition, an association between OSA risk status and diabetic autonomic neuropathy will be explored, given that this diabetes complication has been previously related to OSA [52]. Furthermore, prevalence and correlates of daytime sleepiness and other sleep disturbances, as determined by two additional screening tools, the Epworth Sleepiness Scale and the Pittsburgh Sleep Quality Index, which the EDC participants have completed for the first time during this 25-year follow-up, will also be explored.

6.4 PUBLIC HEALTH SIGNIFICANCE

The high OSA risk prevalence in this study population, as well as in the previously mentioned studies of adults with type 1 diabetes, is alarming. In addition to the previously recognized burden of undiagnosed OSA in the general population, our study showed that a potentially unrecognized burden of OSA among individuals with type 1 diabetes might also exist. Considering the ease of screening, availability of treatment, as well as the adverse consequences of OSA, this disorder constitutes a good public health target for early recognition and prevention among individuals who are already burdened with a serious chronic disease such as type 1 diabetes. Furthermore, two previous studies observed that effective CPAP treatment gradually decreased healthcare utilization costs among both men [53] and women [54] suffering from OSA syndrome (i.e. OSA with the symptoms of daytime sleepiness). Specifically, the number of annual physician visits for male

participants (N=342, age 48.2 ± 10.7 years) were high in the year before they were diagnosed with OSA syndrome (9.21 ± 0.44), but gradually decreased by the fifth year after diagnosis and CPAP therapy by 1.03 ± 0.49 (95%=CI -1.99, -0.07, p< 0.0001), which translated to a 13.92 ± 27.94 (95% CI= -68.68, -40.83, p= 0.0009) Canadian dollar reduction in physician fees [53]. Similarly, the number of annual clinic visits for 231 CPAP compliant female participants (age 50.3 ± 0.7 years) with OSA syndrome increased in the two years prior to diagnosis by 2.30 ± 0.57 and then decreased during the two years after diagnosis by 1.56 ± 0.55 visits (p<0.0001) [54]. This translated to a 20.96 ± 26.60 (p< 0.01) Canadian dollar reduction in physician fees [54]. However, effective CPAP therapy not only gradually decreased healthcare utilization costs [53-54], but it also had beneficial effects on reducing high blood pressure [55], new cardiovascular events [51], and even cardiovascular death among men [56] in other investigations. Thus, OSA screening may reduce social and financial burden, healthcare resources, as well as productivity lost due to further complication development often present in those with diabetes.

While early OSA recognition and treatment in type 1 diabetes populations warrants great attention, reduction and prevention of risk factors associated with OSA might be of even greater public health importance. In fact, our study found that modifiable risk factors (i.e. BMI, HDLc, DBP, and smoking history) were independently associated with the OSA risk status. Improving such risk factors through embracing healthier lifestyle choices (e.g. exercising, eating a healthier, more balanced diet, and smoking cessation) may reduce OSA risk among individuals suffering from type 1 diabetes, not only by improving their wellbeing, but also by reducing the subsequent risk of developing further complications. However, future prospective studies are necessary to explore such a hypothesis, particularly due to the rapidly increasing rates of overweight and obesity in this population [28].

This study also found that hard CAD was associated with OSA risk in women. Although, once present hard CAD is not reversible, the aforementioned lifestyle choices can also be practiced to prevent incident CAD in female individuals [57-58], specifically through decreasing trans unsaturated fat intake [57] and increasing physical activity [58]. For instance, Hu et al. (1997) prospectively followed 80,082 women from the Nurses' Health Study for 14 years (ages 34-59 years, no known history of CAD, stroke, cancer, high cholesterol, or diabetes in 1980) and observed that each 2% energy intake increase from trans unsaturated fats was associated with a 93% increase in the risk of developing heart disease (relative risk 1.93, 95% CI=1.43, 2.61, $p < 0.001$) as compared to the equal energy intake from carbohydrates [57]. Manson et al. (1999) also prospectively followed the Nurses' Health Study participants (N=72,488, ages 40-65 years, no known history of CAD or cancer in 1986) for eight years and observed a strong inverse relationship between physical activity and the risk for coronary events [58]. Namely, female participants in the top four quintiles for energy expenditure (increasing from the lowest quintile) had the following relative risks in comparison to the women in the lowest physical activity quintile group: 0.88, 0.81, 0.74, 0.66, respectively (p for trend = 0.002), independent of their age, BMI, smoking status, alcohol consumption, menopausal status, familial history of hard CAD events, HTN, history of diabetes, history of high cholesterol, and other relevant covariates [58]. Furthermore, as previously discussed, among those persons with established CAD, effective OSA treatment may also reduce new cardiovascular events [51].

In conclusion, high OSA risk prevalence in our type 1 diabetes cohort, along with its modifiable correlates, deserves closer attention and further exploration.

APPENDIX: THE BERLIN QUESTIONNAIRE

The following questions were completed by the Epidemiology of Diabetes Complications Study participants during their 25th-year clinical examination (2011-2014). In addition, a trained research assistant obtained a participant's body mass index and blood pressure.

1. Do you snore?
   _____ Yes
   _____ No
   _____ Don't know

If you snore:

2. Your snoring is…
   _____ Slightly louder than breathing
   _____ As loud as talking
   _____ Louder than talking
   _____ Very loud – can be heard in next room

3. How often do you snore?
   _____ Nearly every day
   _____ 3-4 times a week
   _____ 1-2 times a week
   _____ 1-2 times a month
   _____ Never or nearly never

4. Has your snoring ever bothered other people?
   _____ Yes
   _____ No

5. Has anyone noticed that you quit breathing in your sleep?
   _____ Nearly every day.
   _____ 3-4 times a week
   _____ 1-2 times a week
   _____ 1-2 times a month
   _____ Never or nearly never

6. How often do you feel tired or fatigued after your sleep?
   _____ Nearly every day
   _____ 3-4 times a week
   _____ 1-2 times a week
   _____ 1-2 times a month
   _____ Never or almost never

7. During your wake time, do you feel tired, fatigued or not wake up to par?
   _____ Nearly every day
   _____ 3-4 times a week
   _____ 1-2 times a week
   _____ 1-2 times a month
   _____ Never or almost never

8. Have you ever nodded off or fallen asleep while driving a vehicle?
   _____ Yes
   _____ No

9. If yes, how often does it occur?
   _____ Nearly every day.
   _____ 3-4 times a week
   _____ 1-2 times a week
   _____ 1-2 times a month
   _____ Never or nearly never

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