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SCIENTIFIC INVESTIGATIONS

Polysomnographic predictors of incident diabetes and pre-diabetes: an analysis of the DREAM study

Brian S. Wojeck, MD, MPH[1]; Silvio E. Inzucchi, MD[1]; Li Qin, PhD[2]; Henry Klar Yaggi, MD, MPH[3,4]

[1]Yale University Department of Internal Medicine, Section of Endocrinology, New Haven, Connecticut; [2]Yale University Department of Internal Medicine, Section of Cardiology, New Haven, Connecticut; [3]Yale University Department of Internal Medicine, Section of Pulmonary, Critical Care, and Sleep Medicine, New Haven, Connecticut; [4]The Clinical Epidemiology Research Center (CERC), VA Connecticut Healthcare System, West Haven VA, West Haven, Connecticut

Study Objectives: We sought to evaluate sleep measures that better predict incident diabetes and prediabetes in a large cohort of veterans.

Methods: This secondary analysis included 650 patients without baseline diabetes from a multisite observational veterans' cohort. Participants underwent obstructive sleep apnea evaluation via laboratory-based polysomnography between 2000 and 2004 with follow-up through 2012. The primary outcomes were prediabetes and diabetes defined by fasting blood glucose, hemoglobin A1c, or use of glucose-lowering medication at study initiation. Exposure variables included respiratory event frequency, arousals, and oxygen desaturation. Cox models adjusted for body mass index, age, race, sex, change in body mass index, and continuous positive airway pressure device utilization.

Results: The adjusted analysis revealed that time spent with oxygen saturation less than 90 [hazards ratio (HR) 1.009], confidence interval (CI) 1.001–1.017, $P = .02$), respiratory arousals (HR 1.009, CI 1.003–1.015, $P < 0.01$) and total arousals (HR 1.006 CI 1.001–1.011 $P = .02$) were associated with an increased incidence of diabetes. Increases in mean nocturnal oxygen saturation were associated with decreased incidence of diabetes (HR 0.914 CI 0.857–0.975, $P < .01$) and prediabetes (HR 0.914 CI 0.857–0.975, $P < .01$). No significant relationships were demonstrated for apnea-hypopnea index (AHI), measures related to central apnea, Cheyne-Stokes respiration, periodic limb movements, or Epworth Sleepiness Scale score.

Conclusions: There was no significant association of incident prediabetes or diabetes with AHI, the gold standard of sleep apnea severity. This study suggests that hypoxia may be a better predictor of glycemic outcomes than AHI in an obstructive sleep apnea population and may provide clues to the underlying mechanism(s) that link sleep-disordered breathing and its metabolic consequences.

Keywords: obstructive sleep apnea, OSA, diabetes mellitus, DM, pre-diabetes, CSA, central sleep apnea

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep-disordered breathing has been frequently linked to diabetes mellitus type 2. We sought to evaluate the polysomnographic features that predict the development of pre-diabetes and type 2 diabetes mellitus to better understand the pathogenesis of dysglycemia as it relates to sleep-disordered breathing.

Study Impact: In this longitudinal study of veterans referred for sleep studies, we found that a greater duration of time spent with oxygen saturation <90%, increases in respiratory and total arousal indices were associated with increased rates of incident diabetes. Lower nocturnal oxygen saturation was predictive of incident pre-diabetes and diabetes.

INTRODUCTION

The metabolic consequences of sleep-disordered breathing are an unmet public health challenge. Obstructive sleep apnea (OSA) has a high and rising prevalence in the general adult population (approximately 22% in men and 17% in women),[1] attributable in part to increasing obesity rates as well as general enhanced awareness. OSA is induced by recurrent upper airway collapse resulting in intermittent hypoxemia and awakenings, leading to sleep fragmentation, which is associated with sympathetic activation, systemic inflammation, oxidative stress, and adipokine dysregulation.[2] Many of these features are considered diabetogenic, and, indeed, OSA has been linked to increased prevalence and severity of type 2 diabetes.[3]

The prevalence of OSA is higher among veterans because risk factors for OSA are more prevalent in this population, specifically increasing age, male sex, obesity, and alcohol use.[4–7] There have been multiple cross-sectional studies showing that OSA has been associated with impaired glucose tolerance independent of underlying obesity.[8] A longitudinal study of men without diabetes showed that OSA was an independent predictor of the development of insulin resistance,[9] a fundamental metabolic abnormality considered a strong etiologic factor in the development of prediabetes and type 2 diabetes. OSA has also been associated with certain vascular events more common in patients with diabetes, including myocardial infarction and stroke.[10,11] Other studies have suggested worsening renal disease, neuropathy, and retinopathy in individuals with coexisting diabetes and OSA.[12–15]

The understanding of polysomnographic features that predict adverse health outcomes remains poorly developed. The diagnosis, severity, and management of OSA are based primarily on the apnea-hypopnea index (AHI). Most epidemiologic studies have used the AHI as the primary polysomnographic metric when testing the association between OSA and medical comorbidities. This common assessment of sleep apnea severity, however, correlates poorly with symptom severity.[16–19] Moreover, it does not account for important OSA features such as hypoxemia, arousal index, Cheyne-Stokes respiration, sleep architecture, among others. Furthermore, AHI alone does not appear to be the best predictor for clinically relevant outcomes, such as the development of hypertension, metabolic dysfunction, cardiovascular events, and survival.[20,21] There is evidence that diabetes incidence may be associated with hypoxemia to a greater degree than with AHI.[22] By understanding the pathogenic mechanisms of OSA we can better understand how it is associated with other conditions, specifically diabetes. Furthermore, by evaluating the consistent predictors of prediabetes and diabetes, we can better understand the mechanistic underpinnings of OSA-related dysglycemia. The overall objectives of this study were to determine polysomnographic predictors of prediabetes and diabetes in a large cohort of veterans who have undergone evaluation for sleep-disordered breathing.

METHODS

Overall study design

This was an analysis of the Determining Risk of Vascular Events by Apnea Monitoring (DREAM) study with a goal of evaluating frequency and predictors of incident diabetes and prediabetes in a population of US veterans suspected of having OSA. The goal of the original study was to develop a prognostic model for cardiovascular outcomes, based on physiologic variables related to breathing, sleep architecture, and oxygenation measured during polysomnography. The DREAM study was a multisite, observational cohort study conducted at three Veterans Affairs (VA) centers (West Haven, CT; Indianapolis, IN; Cleveland, OH). Veterans who underwent polysomnography between January 1, 2000 and December 31, 2004, were included based on referral for evaluation of sleep-disordered breathing, documented history and physical prior to sleep testing, and polysomnography. Patients were not included if they were referred for reasons other than evaluation of sleep-disordered breathing. Polysomnographic measures were evaluated and recorded via overnight full attended polysomnography.

Polysomnograms that were recorded outside of West Haven, CT were rescored at the West Haven VA to ensure consistent scoring criteria of all sleep studies. If polysomnogram was performed as a split-night study, only the diagnostic portion was used to diagnose sleep-disordered breathing. Patients were defined as adherent if they had ongoing evidence of continuous positive airway pressure (CPAP) use in the medical record. Nonadherence with CPAP was defined as never receiving CPAP or stopping CPAP in the medical record.

Laboratory evaluation occurred at the beginning and end of the study period and included measures of glycemia, lipid levels, and kidney function. Prognostic sleep variables were abstracted from individually scored sleep studies. The electronic medical record (Vista Web) and VA electronic medical databases, (VA-Medicare data file [VIReC], VA Vital Status file) were used to evaluate baseline characteristics and follow-up of outcomes. The race was recorded as Black, White, Hispanic, or other. The rate of missing race/ethnicity data used was 5–6%. To reduce the rate of missing data, race data were supplemented using the VA-Medicare data file and the VA Vital status file. Socioeconomic status was estimated using each patient's eligibility for VA services.[23] Designation of sleep apnea treatment occurred through clinic record documentation and prosthetic service billing data. Laboratory studies were drawn at the beginning and end of the study period. For this secondary analysis, participants without a baseline diagnosis of diabetes and prediabetes were followed through December 31, 2007 for the development of both prediabetes and diabetes.

Inclusion criteria

Eligible patients included those referred for suspected sleep-disordered breathing who had a history and physical documented in the electronic medical record prior to the sleep study and underwent at least 2 hours of attended sleep monitoring using full polysomnography.

Exclusion criteria

Patients were excluded if they had a history of diabetes at baseline, defined as A1c ≥ 6.5% or fasting blood glucose ≥ 126 mg/dL or the use of glucose-lowering medications prevalent at the time of the initial study recruitment (metformin, sulfonylureas, thiazolidinedione, or insulin). For the prediabetes endpoints, patients were excluded if they had prediabetes or diabetes defined as A1c ≥ 5.7% or fasting blood glucose ≥ 100 mg/dL.

Exposures/sleep measurements

All participants underwent an attended overnight polysomnography. The recording montage consisted of C_3/A_2 and C_4/A_1 electroencephalograms, a bipolar submental electromyogram, thoracic and abdominal inductance plethysmography, airflow via nasal-oral thermocouple, nasal pressure via nasal canula, oximetry, electrocardiogram, body position via mercury gauge sensor, bilateral leg movements via Piezo electric sensors, right and left electro-oculograms. Each study was scored by a certified sleep technologist. Sleep staging and arousals were scored in 30-second epochs utilizing a combination of Rechtschaffen and Kales criteria and criteria from the American Sleep Disorders Association.[24,25] Apneas were defined as near complete reduction in thermocouple lasting > 10 seconds. Apneic events were defined as obstructive if there was evidence of effort in the thoracic belts and central if effort was absent. Hypopneas were defined as ≥30% reduction in thermocouple flow lasting ≥10 seconds associated with a 4% desaturation or ≥50% reduction in nasal flow with a 3% desaturation. Periodic limb movements were defined as an 8-μv increase in the amplitude of the anterior tibialis electromyogram from baseline for 0.5 to 10 seconds for a minimum of 4 movements in succession separated by 5–90 seconds. The periodic limb movement index was defined

as the total amount limb movement events per hour.[26] Each patient's height and weight were recorded prior to overnight polysomnography and used to calculate body mass index (BMI). Race and socioeconomic status were extrapolated from the Patient Treatment File, a VA administrative database that contains demographic characteristics.

Potential predictive clinical sleep factors consisted of multiple polysomnographically derived indices of sleep apnea severity including the AHI, percent of the time with oxyhemoglobin saturation below 90%, average oxygen saturation, minimum oxygen saturation, arousal index, arousals associated with respiratory events, and sleep efficiency. These variables were selected based on plausible biologic pathways by which sleep apnea may lead to dysglycemia.[27–30] Hypoxia has been associated with decreased insulin sensitivity, increased hepatic glucose production, beta-cell failure, and sympathetic activation all of which have been associated with diabetes.[27–30] Apneic events are also associated with sympathetic activation, which has been associated with diabetes.[27–30] In addition to these variables, the Epworth Sleepiness Scale, a common clinical measure of sleepiness, was also evaluated as a predictive variable.[31] As many of the studies included were split-night studies, in which CPAP was utilized once a patient reached an AHI threshold, sleep architecture as a measure of total sleep time was difficult to interpret and therefore was excluded from the final analysis.

Outcomes

The primary outcome was the endpoint of incident diabetes. Time-to-event was defined as the time from overnight polysomnography to the time of a patient's confirmed diagnosis of diabetes, or the end of follow-up. Incident diabetes was defined as the development of glycated hemoglobin or hemoglobin A1c ≥ 6.5% or fasting plasma glucose ≥ 126 mg/dL or prescription for any glucose-lowering medication after the baseline visit in those without any of these criteria at baseline. In this analysis, the initial patient population included study participants that did not have diabetes at baseline (n = 650), with the outcome of developing diabetes (n = 650). This analysis is referred to as incident diabetes analysis (**Table 1**, **Table 2**, and **Table 3**).

The secondary outcome was the endpoint of incident prediabetes among patients without diabetes or prediabetes at baseline. Time to event was defined as the time from overnight polysomnography to the time of a patient's confirmed diagnosis of prediabetes or the end of follow-up. Prediabetes was defined as hemoglobin A1c 5.7–6.4% or fasting plasma glucose 100–125 mg/dL in those patients with normal values for both parameters and no prior history of diabetes or use of glucose lowering medications at baseline.

In this analysis, the initial population included only study participants that did not have diabetes or prediabetes at baseline, with the outcome of developing prediabetes (n = 269). This analysis is referred to as incident prediabetes analysis (**Table 4** and **Table 5**). Potential confounders were evaluated via chi-square (**Table S1** and **Table S2** in the supplemental material).

Data analysis

The goal of this investigation was to select sleep measures that were predictive of prediabetes or diabetes. Based on previously published studies, variables were chosen to develop a "sleep axis". This axis approach is an accepted means of variable reduction, providing a strategy to select important variables.[32–34] The first analysis evaluated predictive polysomnographic features of incident diabetes. The baseline characteristics of this sample were assessed, and an unadjusted analysis was performed between the covariates, exposure, and outcome variable to evaluate for potential confounders. Subsequently, an adjusted analysis was then performed evaluating the relationship of each variable with incident diabetes (as defined by the inclusion criteria) utilizing a Cox proportional hazards analysis, that adjusted for BMI, race, sleep apnea treatment status, socioeconomic status, and sex. The second analysis evaluated predictive polysomnographic features of incident prediabetes. The study population was restricted to patients without diabetes at baseline within the DREAM cohort (n = 650) for the analysis of incident diabetes. The study population was restricted to patients without prediabetes or diabetes at baseline within the DREAM cohort (n = 451) for the analysis of incident prediabetes to evaluate for confounders. When evaluating predictors of developing prediabetes patients with incident diabetes were excluded (n = 269). Hazards ratios and 95% confidence intervals were calculated from the proportional hazards model regression coefficients and standard errors. A P value less than .05 was considered statistically significant.[35–38]

Table 1—Demographics of incident diabetes analysis study population (n = 650).

Age, years, mean ± SD	57.3 ± 11.8
Sex, n (%)	
Male	615 (94.6%)
Female	35 (5.4%)
Race, n (%)	
White	512 (78.8%)
Black	80 (12.3%)
Hispanic or other	58 (8.9%)
BMI, mean ± SD	33.9 ± 6.6
Epworth Sleepiness Scale, (n) mean ± SD	(323) 11.1 ± 5.6
AHI, events/h, mean ± SD	24.1 ± 28.0
Arousal index, events/h, mean ± SD	44.1 ± 29.4

(n) described separately in demographics with missing data. AHI = apnea-hypopnea index. BMI = body mass index.

RESULTS

Sample characteristics

The analytic sample consisted of 650 patients from the parent DREAM study without a diagnosis of diabetes at baseline. This sample had an average age of 57 years (57.3 ± 11.8). The population was predominantly male (94.6%) and White (78.8%). On average, patients were obese with a mean BMI of 33.9 ± 6.6 kg/m^2. On average, patients had mild daytime symptoms based on an Epworth Sleepiness Scale (mean 11) with a great deal of variability

Table 2—Unadjusted baseline characteristics for incident diabetes analysis (n = 650).

Baseline Characteristic	No Diabetes (n = 468)	Incident Diabetes (n = 182)	*P*
ESS, (n) mean ± SD	(231) 11.1 ± 5.8	(92) 11.1 ± 5.3	.98
Split-night study, n (%)	204 (51.3)	109 (68.1)	< .01
Supine apneas index, events/h, mean ± SD	0.1 ± 0.2	0.2 ± 0.4	< .01
CPAP use, n (%)	148 (31.6)	77 (42.3)	.01
Respiratory arousal index, events/h, mean ± SD	22.0 ± 24.8	31.9 ± 29.6	< .01
Spontaneous arousal index, events/h, mean ± SD	17.4 ± 12.6	17.5 ± 11.7	.99
Total arousal index, events/h, mean ± SD	41.6 ± 28.0	50.6 ± 31.8	< .01
Snoring index, events/h, mean ± SD	0.3 ± 0.4	0.3 ± 0.5	.11
Obstructive apnea index, events/h, mean ± SD	0.2 ± 0.4	0.3 ± 0.4	.01
Central apnea index, events/h, mean ± SD	1.5 ± 4.9	2.1 ± 6.2	.19
Hypopnea index, events/h, mean ± SD	9.0 ± 11.0	12.5 ± 13.9	< .01
Cheyne-Strokes pattern, n (%)	11 (2.4)	10 (5.5)	.05
PLM index, events/h, mean ± SD	0.2 ± 0.4	0.1 ± 0.3	.20
Desaturation > 4% index, events/h, mean ± SD	19.1 ± 23.1	26.9 ± 26.5	< .01
Oxygen desaturation nadir, mean ± SD	83.3 ± 7.2	81.4 ± 7.4	< .01
T = 60–89%_INDEX, % of TST, mean ± SD	8.2 ± 16.9	13.4 ± 21.0	< .01
T = 90–99%_INDEX, % of TST, mean ± SD	90.5 ± 18.4	86.3 ± 20.3	.01
Mean nocturnal oxygen saturation, mean ± SD	92.9 ± 2.8	92.0 ± 4.0	< .01
Night oxygen requirement during sleep study, liters, (n) mean ± SD	(20) 2.4 ± 0.9	(8) 2.3 ± 0.5	.65
Chronic oxygen requirement, n (%)	22 (4.8)	9 (5.0)	.84
Apnea-hypopnea index, events/h, mean ± SD	21.7 ± 26.1	30.3 ± 31.5	< .01

(n) described separately in demographics with missing data. CPAP = continuous positive airway pressure, ESS = Epworth Sleepiness Scale, PLM = periodic limb movement.

in symptom scores (standard deviation 5.6). The mean AHI was 24.1 events/h (median 11.7), with a significant degree of variability (standard deviation 28.0). The mean arousal index was elevated at 44.1 (**Table 1**). The second analytic sample consisted of 269 patients from the parent DREAM study without a diagnosis of diabetes or prediabetes at baseline evaluating the outcome of prediabetes. This sample had an average age of 57 years (57.2 ± 12.5). The population was predominantly male (94.4%) and White (78.4%). On average, patients were obese with a mean BMI of 32.1 ± 6.1 kg/m^2. On average, patients had mild daytime symptoms based on an Epworth Sleepiness Scale (mean 11.7) with a great deal of variability in symptom scores (standard deviation 5.8). The mean AHI was 21.3 events/h. The mean arousal index was elevated at 40.0.

Predictors of diabetes

The initial unadjusted analysis of various polysomnographic predictors demonstrated significant associations between respiratory arousals, total arousals, obstructive apnea index, hypopnea index, Cheyne-Stokes pattern, desaturation index, low nocturnal desaturation events, percent of total sleep time spent below 90%, time spent above 90%, lower mean nocturnal oxygen saturation, and apnea-hypopnea index with type 2 diabetes mellitus (**Table 2**). As expected, BMI also predicted patient incident diabetes (supplemental material). After adjusting BMI, change in BMI over time, age, race, sex, depression, and CPAP use, direct measures of hypoxia and arousal remained significantly associated with the outcome. There was a 9% [hazard ratio (HR) 1.009, confidence interval (CI) 1.001–1.017, P = .0228) increase in the risk of incident diabetes per 10% increase of total sleep time spent at an oxygen saturation < 90%. There was also a 9% (HR 1.009, CI 1.001–1.017, P = .02) increased risk of developing diabetes for each 10 event increase in respiratory arousals per hour. For each 10% increase in mean nocturnal oxygen saturation, there was a 67% (HR 0.933 CI 0.886–0.983, P < .01) risk reduction in incident diabetes. There was no significant effect, however, found in relation to AHI, central apnea, Cheyne-stokes respiration, periodic limb movements, or Epworth Sleepiness Scale score (**Table 3**).

Predictors of prediabetes

In an unadjusted analysis, data showed significant associations were observed between the oxygen desaturation index (4%), the oxygen saturation nadir, time spent with oxygen saturation < 90%, respiratory arousal index, supine apnea index, and apnea-hypopnea index (supplemental material). After adjustment for change in BMI over time, age, race, sex, depression, and CPAP use, only mean nocturnal oxygen saturation remained significant. For each 10% increase in mean nocturnal oxygen saturation, there was an 86% (HR 0.9124 CI 0.854–0.974, P < .01) risk

Table 3—Adjusted predictors of incident diabetes analysis via Cox-Regression correcting for baseline BMI, age, race, sex, change in BMI over time, depression, and CPAP use (n = 650).

Baseline Characteristic	Hazard Ratio (95% CI)	*P*
ESS	1.016 (0.976–1.059)	.44
Supine apnea index, events/h	1.496 (0.962–2.324)	.07
Respiratory arousal index, events/h	1.009 (1.003–1.015)	< .01
Spontaneous arousal index, events/h	1.000 (0.988–1.013)	.96
Total arousal index, events/h	1.006 (1.001–1.011)	.02
Snoring index, events/h	0.900 (0.578–1.399)	.64
Obstructive apnea index, events/h	1.128 (0.764–1.665)	.54
Central apnea index, events/h	1.017 (0.992–1.043)	.18
Hypopnea index, events/h	1.009 (0.998–1.020)	.11
Cheyne-Strokes pattern	1.291 (0.595–2.805)	.52
PLM index, events/h	0.697 (0.409–1.188)	.18
Desaturation > 4% index, events/h	1.001 (0.995–1.008)	.71
Oxygen desaturation nadir	1.005 (0.983–1.027)	.69
T=60–89%_INDEX, % of TST	1.009 (1.001–1.017)	.02
T=90–99%_INDEX, % of TST	0.996 (0.989–1.004)	.36
Mean nocturnal oxygen saturation	0.933 (0.886–0.983)	< .01
Oxygen at night, liters	1.799 (0.144–22.442)	.65
Chronic oxygen requirement	1.824 (0.836–3.977)	.13
Apnea-hypopnea index, events/h	1.003 (0.998–1.009)	.23

(n) described separately in demographics with missing data. BMI = body mass index, CPAP = continuous positive airway pressure, ENT = ear, nose, and throat, ESS = Epworth Sleepiness Scale, MAD = mandibular advancement device, PLM = periodic limb movement.

reduction in incident prediabetes. There was not a significant effect found in relation to AHI, central apnea, Cheyne-stokes respiration, periodic limb movements, or Epworth Sleepiness Scale score (**Table 5**).

DISCUSSION

Other studies have also observed an association between various sleep-disordered breathing metric and dysglycemia. For example, in the Sleep Heart Health Study, AHI, lower average oxygen saturation, and time spent at oxyhemoglobin saturation < 90% were associated with elevated fasting blood glucose levels and 2-hour plasma glucose during oral glucose tolerance testing. There was a trend that suggested that mean oxygen saturation may be most predictive of elevated fasting plasma glucose.[39] Intermittent hypoxia in animal models has been shown to decrease insulin sensitivity and increase hepatic glucose production, both of these metabolic abnormalities are considered to be diabetogenic.[27] Using both human and animal models, it has also been demonstrated that intermittent hypoxemia is associated with sympathetic activation, which drives both of these processes. Sleep fragmentation in such models has led to

Table 4—Demographics of incident prediabetes analysis study population (n = 269).

Characteristics	(n = 269)
Age, years, (n) mean ± SD	(269) 57.2 ± 12.5
Sex, n (%)	
Men	254 (94.4%)
Women	15 (5.6%)
Race, n (%)	
White	211 (78.4%)
Black	33 (12.3%)
Hispanic or other	25 (9.3%)
BMI, (n) mean ± SD	(256) 32.1 ± 6.1
Epworth Sleepiness Scale, (n) mean ± SD	(145) 11.7 ± 5.8
AHI, events/h, (n) mean ± SD	(269) 21.3 ± 25.3
Arousal index, events/h, (n) mean ± SD	(269) 40.0 ± 26.7

(n) described separately in demographics with missing data. AHI = apnea-hypopnea index.

Table 5—Adjusted predictors of prediabetes via Cox-Regression correcting for baseline BMI, age, race, sex, change in BMI over time, CPAP use and depression.

Baseline Characteristic	Hazard Ratio (95% CI)	*P*
ESS	1.013 (0.968–1.061)	.56
Supine apnea index, events/h	1.376 (0.612–3.092)	.44
Respiratory arousal index, events/h	1.004 (0.997–1.012)	.26
Spontaneous arousal index, events/h	0.990 (0.976–1.004)	.17
Total arousal index, events/h	1.001 (0.995–1.007)	.77
Snoring index, events/h	1.115 (0.644–1.928)	.70
Obstructive apnea index, events/h	1.036 (0.611–1.758)	.89
Central apnea index, events/h	1.014 (0.967–1.063)	.56
Hypopnea index, events/h	1.005 (0.991–1.019)	.51
Cheyne-Strokes pattern	2.476 (0.850–7.217)	.10
PLM index, events/h	1.106 (0.672–1.818)	.69
Desaturation > 4% index, events/h	1.005 (0.996–1.013)	.28
Oxygen desaturation nadir	0.984 (0.957–1.012)	.26
T = 60–89%_INDEX, % of TST	1.005 (0.994–1.016)	.35
T = 90–99%_INDEX, % of TST	0.994 (0.983–1.004)	.23
Mean nocturnal oxygen saturation	0.912 (0.854–0.974)	< .01
Oxygen at night, liters	—	—
Chronic oxygen requirement	1.024 (0.244–4.302)	.97
Apnea-hypopnea index, events/h	1.001 (0.994–1.009)	.77

BMI = body mass index, CPAP = continuous positive airway pressure, ESS = Epworth Sleepiness Scale, PLM = periodic limb movement.

adiposity, insulin resistance, and hyperglycemia.[40–43] In one study, an increased risk of insulin resistance was observed among healthy adults who underwent 5 hours of intermittent hypoxia during wakefulness.[44] Several studies of chronic hypoxia have also demonstrated that both impaired glucose tolerance and type 2 diabetes occur at a higher frequency in people residing at higher altitudes, thought to be at least partly related to hypoxia.[28–30,45] In a study by Larsen et al[28] participants residing at sea level at baseline had a doubling of their insulin resistance as measured by euglycemic clamp compared to when they were evaluated at 4,599 feet above sea level. In this same study, there was evidence of higher levels of norepinephrine at higher altitudes, suggesting at least 1 potential mechanistic connection to hypoxemia. Furthermore, hypoxemia has been linked to progressive beta-cell failure in animal models.[42,46]

Our study suggests that maintaining a higher nocturnal oxygen saturation significantly decreases incident prediabetes and diabetes. This infers a consistent pathogenesis of hypoxemia on these progressive and interrelated dysglycemic states. Both respiratory and total arousal indices were also associated with incident diabetes. This finding is consistent with the current understanding of pathophysiology associated with arousals, specifically its association to increase circulating concentrations of catecholamines, which, as counter-regulatory factors, may promote hyperglycemia.[47–49]

Strengths of this study include the use of full attended polysomnography, longitudinal follow-up, and including prediabetes as outcome variable, and including a wide spectrum of severity of sleep-disordered breathing, enhancing generalizability.

Several limitations of the study should also be considered. First, the study population was comprised of veterans, who may be at higher baseline risk for developing dysglycemic conditions due to higher rates of obesity and alcohol use.[6,7] Second, although we adjusted for race, BMI, and sex, the study population did skew toward a predominantly White, obese, and male study population, thereby limiting generalizability. Glycemic measures used were fasting plasma glucose and A1c, employed together to determine if patients developed prediabetes or diabetes. Although both measures are diagnostic, they reflect different aspects of glycemia, and we did not assess routinely for concordance between them. Moreover, at the time this cohort was developed, we did not confirm the diagnosis of diabetes with a second test (as is now recommended in guidelines from the American Diabetes Association).[50] However, such potential misclassification of the outcome would tend to bias the results toward the null hypothesis and would not explain our observation. The Epworth Sleepiness Scale score was not consistently documented in the electronic health record at all 3 sleep centers in this retrospective observational cohort study designed to examine the impact of polysomnographic variables on health outcomes. BMI is known to be a crude measure of adiposity, whereas waist-to-hip ratios are better measures of the effect of adiposity on sleep-disordered breathing. This study was retrospective, and other measures of adiposity were not routinely measured at the study sites, which limits assessment of obesity.[51] This study was retrospective, and other measures of adiposity were not routinely measured at the study sites, which limits assessment of obesity. Although it would have been helpful to know the reason different patients were referred for polysomnography, these data were not available. This study did include 2 patients who did not tolerate CPAP who went on to alternative treatments. One patient was treated with mandibular advancement and one patient with otolaryngology intervention, neither developed diabetes. They were considered CPAP nonadherent in the analysis.[52,53] The definition of adherence was defined as whether patients had used CPAP consistently vs never initiating CPAP or stopping CPAP based on the medical record. These data were collected prior to remote monitoring of CPAP use, therefore, more granular data are unavailable. This definition of CPAP adherence overall would underestimate the effect of PAP therapy and bias toward the null. Patients who had a split-night polysomnogram only utilized the diagnostic portion of the study, which may underestimate rapid eye movement-related apnea-hypopnea; however, to enhance generalizability, these patients were included in the study population. To address this more, we have done an evaluation by dividing patients by full-night polysomnography vs split-night polysomnography for each analysis. These subdivided evaluations were not adequately powered; however, it does not appear that AHI was a significant contributor these analyses stratified by full diagnostic vs split-night diagnostic testing.

Despite these limitations, these data provide further support for the growing recognition of the importance of hypoxia as a potential etiologic factor in the progressive hyperglycemia that marks both diabetes and prediabetes.

CONCLUSIONS

In this longitudinal study of veterans referred for a sleep study, we found that a greater duration of time spent with oxygen saturation < 90% and increases in the respiratory arousal index were associated with incident diabetes. Moreover, a higher mean oxygen saturation during sleep was found to protect against the development of diabetes, a finding that additionally extended to the development of prediabetes. These data suggest that the mechanistic underpinnings linking sleep-disordered breathing and dysglycemic states may relate to nocturnal hypoxemia.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
CI, confidence interval
CPAP, continuous positive airway pressure
DREAM, Determining Risk of Vascular Events by Apnea Monitoring
HR, hazard ratio
OSA, obstructive sleep apnea
VA, Veterans Affairs

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Address correspondence to: Brian S. Wojeck, MD, MPH, Yale University, Section of Endocrinology, 333 Cedar Street, P.O. Box 208020, New Haven, CT 06520; Tel: (480) 703-3344; Fax: (843) 258-1255; Email: Brian.Wojeck@yale.edu

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