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# Obstructive Sleep Apnea and Incident Diabetes: A historical cohort study

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**Title: Obstructive Sleep Apnea and Incident Diabetes: A historical cohort study.**

**Running title:** Obstructive Sleep Apnea and Incident Diabetes

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**Authors' Contributions**

Dr. Tetyana Kendzerska was involved in the following: literature search, study conception and design; ethics boards' application; obtaining administrative data; cleaning, analyses and interpretation of data; drafting of the manuscript.

Dr. George Tomlinson, Dr. Richard Leung, Dr. Andrea Gershon and Dr. Gillian Hawker were involved in the following: study design; data interpretation; drafting of the manuscript; critical revision; and supervision of manuscript writing.

Dr. Andrea Gershon additionally was involved in ethics boards' application, obtaining administrative data and data analyses.

Dr. George Tomlinson additionally was involved in ethics boards' application and data analyses.

Dr. Richard Leung additionally was involved in study conception, ethics boards' application, is an owner of the sleep portion of the Chest Dataset from which the study sample was extracted, and gave final approval of the submitted manuscript.

**Conflicts of interest**

All authors have indicated that they have no financial conflict of interest.

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This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

**At a Glance Commentary**

**Scientific Knowledge on the Subject:**

- Published reports on the causal relationship between OSA and incident diabetes are very limited.
- Among only six longitudinal studies published up to date, five found a significant association between obstructive sleep apnea and incident diabetes.
- However, these studies were generally small, had few events, did not account for time-to-event in their analyses, and employed inconsistent definitions of obstructive sleep apnea.
- There is a need for a larger study with rigorous assessment of both obstructive sleep apnea and diabetes, with sufficient follow-up time to allow development of disease.

**What This Study Adds to the Field:**

- Based on a large clinical cohort, our study shows that among people with obstructive sleep apnea, and controlling for known risk factors for diabetes development, initial obstructive sleep apnea severity predicted risk for incident diabetes: in fully-adjusted models, patients with apnea-hypopnea index > 30 had a 30% higher hazard of developing diabetes than those with AHI < 5.
- Apnea-hypopnea index during rapid eye movement sleep and measures of the physiologic consequences of obstructive sleep apnea (e.g., oxygen desaturation, sleep deprivation and sympathetic activation) were also risk factors for diabetes in this population.
- Risk-stratification of patients with obstructive sleep apnea according to these sleep apnea-related predictors may be useful in identifying those most likely to develop diabetes, allowing timely intervention.

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## ABSTRACT

**Rationale:** Despite emerging evidence that obstructive sleep apnea (OSA) may cause metabolic disturbances independently of other known risk factors, it remains unclear whether OSA is associated with incident diabetes.

**Objective**: To evaluate whether risk of incident diabetes was related to the severity and physiological consequences of OSA.

**Methods and Measurements:** A historical cohort study was conducted using a clinical and provincial health administrative data. All adults without previous diabetes referred with suspected OSA who underwent a diagnostic sleep study at St Michael's Hospital (Toronto, Canada) between 1994 and 2010 were followed through health administrative data until May 2011 to examine the occurrence of diabetes. All OSA-related variables collected from the sleep study were examined as predictors in Cox-regression models, controlling for sex, age, body mass index, smoking status, comorbidities and income.

**Main Results**: Over a median follow-up of 67 months, 1,017 (11.7%) of 8,678 patients developed diabetes, giving a cumulative incidence at five years of 9.1% (95%CI: 8.4% to 9.8%). In fully-adjusted models, patients with apnea-hypopnea index (AHI) > 30 had a 30% higher hazard of developing diabetes than those with AHI < 5. Among other OSA-related variables, AHI in rapid eye movement (REM) sleep, and time spent with oxygen saturation less than 90% were associated with incident diabetes, as were heart rate, neck circumference and sleep time.

**Conclusions**: Among people with OSA, and controlling for multiple confounders, initial OSA severity and its physiologic consequences predicted subsequent risk for incident diabetes.

**Words**: 241


**Key words:** Sleep Apnea, Obstructive; Diabetes Mellitus; Epidemiology

## INTRODUCTION

Diabetes has been described as a public health epidemic, afflicting 10.8% of women and 11.8% of men in the United States (1). There is emerging evidence that obstructive sleep apnea (OSA), through chronic intermittent hypoxemia, recurrent arousals, and neurohumoral changes may cause metabolic disturbances including insulin resistance independently of other known risk factors (2-5) and that OSA may represent a therapeutic target in this condition (6).

It remains unclear whether OSA may lead to incident diabetes (3, 7, 8). Among six longitudinal studies, five found a significant association between OSA and incident diabetes (9-13). However, these studies were generally small, had few events, did not account for time-to-event in their analyses (9, 11, 12) and employed inconsistent definitions of OSA (e.g., apnea-hypopnea index (AHI)≥5 (9), AHI≥8 (10), oxygen desaturation index>5(12, 13)). Further, there has been very limited exploration of the prognostic value of other possibly pathophysiologically relevant OSA-related factors (e.g. arousals, total sleep time) (10). One large community-based study (the Wisconsin Sleep Cohort) reported an association between OSA and prevalent, but not incident diabetes (14). However, the number of events occurring within follow-up time was small to detect a true relationship (n=26), too many predictors for that number of events were included in analyses, and logistic regression used does not take into account the timing of the events. There is a need for a larger study with rigorous assessment of both OSA and diabetes, with sufficient follow-up time to allow development of disease. We evaluated whether risk of incident diabetes was related to the severity and physiological consequences of OSA in a large historical cohort of patients studied with in-laboratory polysomnography over more than a decade and whose health information was obtained through provincial health administrative data. Some of the results of these studies have been previously reported in the form of an abstract (15).

## METHODS

### Study Design

We included patients who were referred with suspected OSA and underwent a first diagnostic sleep study at St. Michael's Hospital (Toronto, Canada) between September 1, 1994 and December 31, 2010. Sleep laboratory clinical data were linked to health administrative data at the Institute for Clinical Evaluative Sciences (ICES, Ontario, Canada) from July 1, 1991 to March 31, 2011. The ethics committees of all institutions involved (St. Michael's Hospital, ICES, University of Toronto) approved the study. Details on cohort description are provided elsewhere (16).

### Data Sources

***Clinical data:*** The St. Michael's Hospital Sleep Lab database includes a large set of clinical, demographic and polysomnographic (PSG) variables that have been collected for research purposes since 1991 (Table E1 ~~in the online data supplement~~). Each patient in the cohort underwent full in-laboratory PSG recording. Disease-specific symptoms and history were collected using standardized questionnaires.

***Health Administrative data:*** Residents of Ontario have universal public health insurance, the Ontario Health Insurance Plan (OHIP), covering all medically necessary services. All Ontario residents are eligible for OHIP coverage after 3 months of residency in the province (17). Legislation prohibits the private delivery of services covered under OHIP, including laboratory testing. Since 1991, ICES has housed high quality administrative data on publicly funded services provided, including individual-level information on physician claims, acute care hospitalization and emergency department visits within Ontario (18). The eligibility of cohort

participants for health insurance and their vital status through the follow-up period were assessed using data from the Registered Persons Database (RPDB). Administrative data regarding claims for continuous positive airway pressure (CPAP) therapy through the Ontario Assistive Devices Program (ADP) (19) have been available since 2004. A further administrative dataset used for this analysis, the Ontario Diabetes Database (ODD), was developed to establish population-based incidence and prevalence of diabetes in Ontario (20, 21). In addition to the usual ICES data from 1991, the ODD captures hospitalizations during the time period 1988-1990. Details of variables derived from administrative datasets and detail descriptions of all datasets used are provided in the online data supplement (Tables E2, E3).

**Study Sample**

Patients who had undergone a first diagnostic sleep study during the defined study period, and who had a diagnosis of OSA (AHI ≥5), or suspected OSA (referred with sleep apnea, but with AHI<5) were extracted from the St. Michael's Hospital database. Patients were excluded if they (i) underwent split-night; had (ii) more than 50% central events or (iii) AHI<5 and a diagnosis of another sleep disorder or (vi) prevalent diabetes, from the ODD, at any time between April 1988 and the diagnostic sleep study.

**Predictors**

The following variables were derived from clinical data and considered as possible predictors in our statistical models: (i) PSG indices— total sleep time (TST), AHI during TST, rapid eye movement sleep (REM-AHI), and non-REM sleep (non-REM-AHI), arousals index, total number of awakenings, mean oxygen saturation ($SaO_2$), duration of $SaO_2$<90% (TiSaO2<90%), mean heart rate (HR), and the percentage of each sleep stage; (ii) clinical symptoms— daytime sleepiness (DS), identified by mean of the Epworth Sleepiness Scale or a positive answer to the

question “During the day, do you ever fall asleep unintentionally?”; and self-reported snoring; (iii) neck circumference; (iv) self-reported family history of OSA or snoring.

The AHI was defined as the number of apneas and hypopneas per hour of sleep. Hypopnea was consistently defined during the study period as: (i) a decrease of more than 50% of the baseline amplitude of breathing for at least 10 seconds; or (ii) a clear but smaller decrease in amplitude for at least 10 seconds that is associated with either an $SaO_2$ drop of ≥3% or an arousal (22). Patients were classified as not having OSA (AHI < 5), or with mild (AHI of 5 to 14.9), moderate (AHI of 15 to 30) or severe (AHI>30) OSA (23).

**Outcome**

The primary outcome was time from the diagnostic PSG to incident diabetes derived from the ODD (20). The ODD employs a validated algorithm which identifies people with diabetes as those having at least one hospitalization record or at least two physician services claims bearing a diagnosis of diabetes within a two-year period. This algorithm is highly sensitive (86%) and specific (97%) for identifying patients in whom diabetes was recorded in primary care charts; positive predictive value is 80% (20). Use of the first service date was considered as the incident diabetes date. Subjects were followed from their first diagnostic sleep study to the end of March 2011, or the occurrence of a primary outcome or all-cause mortality, whichever occurred first.

**Potential confounders**

The following potential confounders were extracted from the Sleep Lab clinical database: age, sex, BMI, waist circumference, self-reported smoking and alcohol consumption. Comorbidities at baseline (stroke, myocardial infarction (MI), chronic heart failure (CHF), hypertension (HTN) and the Johns Hopkins’ aggregated diagnosis groups (ADGs)) were identified from administrative data over a three-year period before the diagnostic sleep study. Comorbidity at

baseline based on ADGs was categorized as low (0 to 5 ADGs), medium (6 to 10 ADGs) or high (≥11 ADGs) (24). Each patient was assigned to an income quintile using the patient's postal code.

**Statistical Analysis**

Descriptive statistics were calculated for relevant data. Crude incidence rates for diabetes per 100 person-years were calculated for the entire sample and by OSA severity (23, 25). In a frail population, death, termed a competing event, may preclude the occurrence of diabetes and lead to overestimation of incidence by the usual Kaplan-Meier method (26). Therefore, we estimated incidence with the cumulative incidence function, which accounts for competing risks. Formal tests for differences in incident diabetes and all-cause mortality between groups were performed using the modified $\chi^2$ statistic (27).

We used multivariable Cox regression models to investigate the relationships between OSA-related predictors and incident diabetes, and expressed the results as hazard ratios (HRs) (28, 29) (more details in the online data supplement). AHI was treated as both a continuous and categorical variable. We used restricted cubic spline (28) transformations for continuous explanatory variables if non-linearity was observed, and the resulting standardized HRs compare the 75th and 25th percentiles. To confirm findings from traditional multivariable Cox-regression model, the Fine and Gray competing-risk regression model was used (30).

For missing variables we used multivariate imputation by chained equations to generate five complete datasets (31) and pooled the coefficients (32). For a unified presentation of all results and figures, the findings shown are for a single imputed dataset. Pooled CIs across imputations for OSA-related variables were at most 2% wider than those presented.

Systematic reviews (8, 33) and expert opinion found age, sex, smoking status, CV comorbidities, BMI, AHI, TST and DS to be important for predicting diabetes, so these variables were forced into the models. Although waist circumference is a more accurate measure of obesity than BMI, BMI was chosen to be included in our statistical model as it improved model fit compared to waist circumference and is easier to obtain in routine clinical practice and less affected by measurement error. Other variables were chosen for inclusion if they were selected by backward step-down variable deletion (34) in at least three imputed datasets. We investigated a priori - defined interactions between AHI and DS, BMI, age, sex and CVD at baseline (8).

We used the bootstrap for internal validation and over-fitting-corrected calibration. Discriminative ability was assessed using Harrell's C-index and predictive ability using the model likelihood ratio $\chi^2$ statistic (28).

To address the concern that the exact time of the incident diabetes is unknown, we used a binomial regression with the complementary log-log link function, which allows incorporation of different follow-up time for each subject in the model to estimate incidence rate ratio (35, 36).

***Sensitivity analysis***. In the post-2004 cohort with information on CPAP claims, the final model was refitted with the addition of a time-dependent CPAP treatment variable (more details in the online data supplement, Figure E1). To assess the effect of OSA-related predictors on an untreated sample, patients were censored at the time of a CPAP claim.

Additional sensitivity analyses included the following: analyses in which only participants who were eligible for OHIP all of each year (i.e., not out of the province during the year) with at least 5 years look-back window and at least 2 years follow-up; all gave the similar results with the main analyses (data not shown). Finally, the statistical models were refitted on the entire sample including participants who underwent split-night study (Table E6).

Finally, to assess the sensitivity of results to unmeasured confounders, we used the approach recommended by Lin et al, 1998 (37).

Additional details on the method are provided in the online data supplement.

All statistical analyses were performed using R version 2.15.2 (http://www.r-project.org) and SAS 9.3.

***Sample size consideration***. We expected between 162 and 1,038 events based on an anticipated sample of 5000 persons with an average of 5 years of follow-up and reported rates of incident diabetes from 0.65 to 4.15 per 100 person-years (9-12, 14). That would allow us to examine at least 16 predictors, using the rule of thumb of 10 events per predictor (38).

## RESULTS

### Sample Characteristics

Between January 1, 1994 and December 31, 2010, 11,596 individuals underwent a first diagnostic sleep study and 10,149 (88%) were linked to administrative datasets (Figure E~~1~~2 ~~in the online data supplement~~). Patients who were not linked had similar OSA severity and demographic characteristics, but fewer CV comorbidities and greater daytime sleepiness (16). Our final analyses included 8,678 participants without diabetes at baseline. Table 1 shows baseline characteristics of patients for the entire sample and by OSA severity. The included sample had 62% males, a median age of 48 years and a median AHI of 15. The amount of missing data ranged from 0.7% (AHI) to10.1% (TiSaO2<90%), 2.4% was missed for BMI and TST, 6.8% - for daytime sleepiness, 7.8% - for heart rate, and 8.2% - for smoking status (16).

### Incidence of diabetes

Over a median follow-up of 67 months, 1,017 (11.7%) participants experienced incident diabetes, giving an incidence rate of 2 per 100 person-years. The potential competing event, death without diagnosed diabetes, occurred in 395 subjects. Cumulative incidence of diabetes at five years for the entire sample was 9.1% (95%CI: 8.4%-9.8%); for patients with mild OSA – 7.5% (6.3%-8.6%), with moderate OSA – 9.9% (8.3%-11.4%), with severe OSA – 14.9% (13.2%-16.6%). The unadjusted difference in incidence of diabetes was significant ($p<0.0001$) between patients with severe OSA and AHI<5.

**Multivariable Cox Regression Models**

Table 2 shows the HR estimates and model fit statistics for the two classes of models we examined, with AHI as a continuous or categorical variable. In fully-adjusted model, severe OSA as defined by AHI was significantly associated with incident diabetes. Patients with severe OSA had a 30% higher hazard of developing diabetes compared to those without OSA, while mild and moderate OSA had a 23% higher hazard (Table 2, Figure 1). Among other OSA-related predictors, REM-AHI, and TiSaO2<90% were consistently associated with incident diabetes (Table 3), as were daytime sleepiness, heart rate in sleep, neck circumference and sleep time (Figure 1, Table E5 ~~in the online data supplement~~). All models were well calibrated (all observed and predicted five-year survival within 2%) and validated (optimism for $R^2$ for all explored models was ≤0.007).

**Competing risk analyses**

In the Fine and Gray regression, the effects of DS, neck circumference, heart rate, and OSA severity on incident diabetes had similar HRs to those from the Cox regression and remained significant, while the effect of sleep time became non-significant.

**Interactions**

The effect of AHI on incident diabetes significantly decreased with increased BMI (p=0.0013) and age (p=0.0326) (Table E5 ~~in the online data supplement~~).

**CPAP treatment effect**

Among 3,931 subjects who underwent a diagnostic PSG between 2004 and 2010, 611 (15.5%) submitted a CPAP claim. Among 267 (6.8%) patients who experienced incident diabetes, 66 claimed CPAP before the incident date (24.7%), and 7 after (2.6%); among the other 3,664 subjects, 538 (14.7%) claimed for CPAP treatment. A claim for CPAP treatment had a non-significant effect in fully-adjusted models on the risk of diabetes (p values > 0.2). When models were refitted on an untreated sample, all predictors except DS remained significantly associated with the outcome.

**Complementary log-log regression model**

After accounting for follow-up time in the binomial regression model, AHI, REM-AHI and TiSaO2<90% remained significant, as did sleep time, DS, heart rate, and neck circumference.

## DISCUSSION

In a large clinical cohort without diabetes at baseline, 11.7% of subjects experienced incident diabetes over a median 67 months of follow-up. The multivariable Cox regression models identified that OSA severity, expressed as AHI, was independently and significantly associated with incident diabetes. In addition, the OSA-related factors REM-AHI and TiSaO2<90% were significant predictors, as were shorter total sleep time, higher mean heart rate, greater neck circumference and the presence of daytime sleepiness. In an untreated subsample, all predictors except DS remained significantly associated with the outcome. The effects of predictors were consistent in a model adjusting for the competing risk of all-cause mortality and in a binomial

regression accounting for imprecision in the date of diagnosis of diabetes. The present study agrees with the much smaller single study that looked at time-to-diagnosis of diabetes by Botros et al (2009), which found an independent association between OSA and incident diabetes after adjusting for multiple confounding factors (10).

Our study addresses limitations of previously published observational studies of OSA and diabetes. Due to its larger size (more than 8,500 patients) and longer period of complete follow-up (more than 10 years), our study was able to analyze a number of events that is more than an order of magnitude larger than occurred in any previous study, including the Wisconsin Cohort Study. Further, this allowed assessment of many OSA-related factors beyond AHI and adequate control for numerous potential confounders impossible in a smaller study. Clinical data were consistently collected and used the same PSG scoring criteria over time. We included patients with a wider range of OSA severity than observed in community-based studies and a relatively large number of females. We used validated algorithms to define prevalent diabetes and comorbidities at baseline, and, finally, used rigorous methods for missing data, model selection, calibration and validation.

Our findings (that longer TiSaO2<90%, shorter sleep time and higher heart rate increase the risk of diabetes) are consistent with proposed pathophysiological mechanisms (oxidative stress caused by intermittent hypoxemia, sleep deprivation or sleep fragmentation, and sympathetic activation) whereby OSA may lead to diabetes. Severity of hypoxemia has been found to be associated with glucose intolerance and insulin resistance (39, 40). Sleep deprivation may act through sympathetic activation and subsequent alterations in hypothalamic-pituitary-adrenal axis (4, 41). Elevated resting heart rate, an indicator of sympathetic nerve activity, has

been shown to be associated with incident diabetes through possible relation between sympathetic activity and insulin resistance (42, 43).

Similarly, neck circumference, a strong clinical predictor of OSA (44) and a significant independent predictor of incident diabetes in our study, has also been associated with impaired glucose homeostasis and cardio-metabolic syndrome (45, 46).

We found that in addition to overall AHI during TST, REM–AHI was also an independent predictor of diabetes. Compared with NREM sleep, REM sleep has been shown to be associated with greater sympathetic activity and respiratory and cardiovascular instability. Apneas during REM sleep lead to greater degrees of hypoxemia and sympathetic activity compared with events in NREM sleep (47). In a cross-sectional study on a predominantly African American and Hispanic cohort, REM-AHI, but not overall AHI, was significantly and independently associated with diabetes (48). Similarly, we found that REM-AHI was significantly associated with incident diabetes and had a larger effect than overall AHI. The clinical importance of AHI in REM may have significant implications for clinical practice (47).

The decreased effect of AHI with age on incident diabetes found in our study has been observed previously for the relationship between OSA and mortality (49). Protective adaptive physiological change through longstanding mild chronic intermittent hypoxia is one of the possible explanations (50). A similar effect on the association between AHI and incident diabetes was found for BMI: the effect of AHI decreased with increasing BMI. It is possible that very obese individuals are already at such high risk for developing diabetes that OSA confers little incremental risk.

There are several limitations that should be considered in the interpretation of our findings. As with any observational study, some methodological issues are related to availability

of data. Some important confounders (e.g., family history of diabetes, race) were not available. The generalizability can be affected by the single center design of our study. Also using the ODD to derive incident diabetes, we were unable to distinguish between Type 1 and Type 2 diabetes. However, we expect the vast majority of events to be Type 2 because of the age of our cohort. Though validated algorithms were used to define prevalent diabetes and prior comorbidities from health administrative data, these algorithms are characterized by certain sensitivity and specificity resulting in possible misclassification of subjects. If differential, bias could go in either direction, while if non-differential (misclassified randomly and independently of disease state), the estimated effect of OSA severity on incident diabetes is more likely to fall below the true value (51, 52). Because of universal health care in Ontario, this measurement error (undiagnosed cases of diabetes in the cohort) was likely independent of the exposure (severe OSA), so we may have underestimated the true effects. With respect to defining incident diabetes cases using the ODD, a small proportion of prevalent cases may be misclassified as incident cases. This may occur when disease was not captured in the administrative health data within observational period prior to baseline for patients with true diabetes. In addition, the date of diagnosed diabetes in administrative data is not the exact time of diabetes development: it could have occurred any time before this date. Using the complementary log-log link regression we tried to address this limitation and have not revealed any important differences compared to the Cox-regression model. Finally, patients with more severe OSA may have more contact with the health care system and may be more likely to be tested for diabetes and consequently diagnosed with diabetes. We addressed this issue by adjusting our models for age, sex, BMI and baseline comorbidities, known predictors of health care utilization for OSA patients (53). Among variables tested in our models, older age, hypertension, and higher income have been also shown

to be associated with a higher likelihood of having a glucose test (54). Further, we assessed the sensitivity of the results to unmeasured confounders and found that only fairly strong confounding reduced the HR of 1.31 sufficiently, that it was no longer statistically significant (details are provided in the online data supplement, Table E4, Figure E3). In particular, the odds ratio between the confounder and OSA severity needed to be 2.5 to 3. Although an unmeasured confounder could be any unmeasured feature of the patient, we were most concerned about screening for diabetes. Since it is implausible that screening occurs 2.5 to 3 times more often in those with AHI > 30 compared to those with AHI < 5, when we have already accounted for age, sex, prior comorbidities and income status, we believe that confounding by diabetes screening is not solely responsible for the observed HR of 1.31. The true HR may be lower than 1.31, but remains statistically significantly elevated for reasonable assumptions about unmeasured confounding~~Further, assessing the sensitivity of results to unmeasured confounders , we found that unmeasured confounders (e.g. screening for diabetes) should increase both the hazard of incident diabetes and the probability of severe OSA (AHI>30 vs. AHI<5) from two and half to three-fold to change the association between incident diabetes and severe OSA from the observed value of 1.31 (95% CI: 1.07-1.61) to non-significant (details are provided in the online data supplement).~~.

The non-significant effect of treatment that we found in the post-2004 cohort could be explained by lack of information about CPAP adherence, treatment approaches other than CPAP, and reduced sample size for this analysis. Also, patients would have been suffering from physiological consequences of OSA for many years before starting treatment that could have increased their risk of developing adverse long-term consequences. Nevertheless, since a treatment effect may attenuate a possible association between OSA and incident diabetes, we

conducted an additional analysis on untreated subsample only. This subsample analysis replicates the results obtained on the entire cohort. Thus, the non-significant association between CPAP claims and the outcome of interest should not be interpreted as a lack of efficacy of CPAP treatment in preventing diabetes as our study was not designed to address this question.

Our study shows that among people with OSA, and controlling for multiple confounders, initial OSA severity predicted risk for incident diabetes. AHI during REM sleep and measures of the physiologic consequences of OSA (e.g., oxygen desaturation, sleep deprivation and sympathetic activation) were also risk factors for diabetes in this population. Risk-stratification of patients with OSA according to these OSA parameters may be useful in identifying those most likely to develop diabetes, allowing timely intervention.



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**Figure legends.**

**Figure 1.** Results from multivariable Cox regression model presented as standardized hazard ratios (comparing 75$^{th}$ percentile to 25$^{th}$ percentile) with shading representing confidence levels (99%, 95%, 90%, 80% and 70%).

ADG – comorbidity defined using aggregated diagnostic groups as low (1), medium (2) or high (3); AHI – apnea-hypopnea index, events/hour; AMI – acute myocardial infarction; BMI – body mass index, kg/m$^2$; daytime sleepiness – identified by a positive answer to the question "During the day, do you ever fall asleep unintentionally?"; HR – heart rate, bpm; income - income quintiles, ranked from poorest (1) to wealthiest (5); NECK – neck circumference, cm; TST – total sleep time, hours.

**Table 1**. Characteristics of patient with a full-night diagnostic sleep study who were linked to the health administrative data: without diabetes at baseline (n=8,678) and with diabetes at baseline (n =1,471)). Median (interquartile range, IQR) or n (%)¥.

| **Variables** | | **With diabetes** (n=1,471) | **Without diabetes** (n=8,678) | **By OSA severity for sample without diabetes** (n=8,678) | | | |
|---|---|---|---|---|---|---|---|
| | | | | AHI<5 (n=1,959) | 5≤AHI<15 (n=2,410) | 15≤AHI≤30 (n=1,975) | AHI>30 (n=2,334) |
| ***Demographic characteristics*** | | | | | | | |
| Male | | 909 (61.8) | 5,377 (62) | 893 (45.6) | 1399 (55.6) | 1238 (62.7) | 1808 (77.5) |
| Age, years | | 59.0 (50.0-68.0) | 48.0 (38.0-58.0) | 42.0 (33.0-51.0) | 47.0 (38.0-57.0) | 50.0 (41.0-59.0) | 51.0 (43.0-61.0) |
| ***Clinical symptoms and findings from physical examination*** | | | | | | | |
| DS*, Yes | | 663 (45.1) | 2,994 (34.5) | 629 (32.1) | 754 (31.3) | 614 (31.1) | 966 (41.4) |
| ESS total (0-24) | | 8.0 (5.0-12.0) | 8.0 (5.0-12) | 8.0 (5.0-12.0) | 8.0 (4.0-12.0) | 8.0 (5.0-12.0) | 8.0 (5.0-12.0) |
| BMI, kg/m$^2$ | | 32.0 (28.1-37.6) | 28.4 (25.1-32.7) | 25.8 (22.9-29.6) | 27.8 (24.8-31.5) | 28.8 (25.7-32.8) | 31.1 (27.5-35.7) |
| Neck circumference, cm | | 41.0 (38.0-44.0) | 39.0 (36.0-42.0) | 37.0 (33.0-39.0) | 38.0 (36.0-41.0) | 40 (37.0-42.0) | 41.0 (39.0-44.0) |
| ***History*** | | | | | | | |
| Smoking status, self-reported | current | 193 (13.1) | 1,646 (19.0) | 377 (19.2) | 476 (19.8) | 342 (17.3) | 435 (18.6) |
| | ex-smoker | 351 (23.9) | 1,518 (17.5) | 263 (13.4) | 373 (15.5) | 362 (18.3) | 501 (21.5) |
| | never | 761 (51.7) | 4,845 (55.8) | 1181 (60.3) | 1354 (56.2) | 1075 (54.4) | 1207 (51.7) |
| Prior HTN | | 1,004 (68.3) | 2,638 (30.4) | 340 (17.4) | 611 (25.4) | 652 (33.0) | 1019 (43.7) |
| Prior AMI | | 159 (10.8) | 241 (2.8) | 26 (1.3) | 50 (2.1) | 58 (2.9) | 106 (4.5) |
| Prior Stroke | | 77 (5.2) | 146 (1.7) | 16 (0.8) | 46 (1.9) | 27 (1.4) | 56 (2.4) |
| Prior CHF | | 282 (19.2) | 336 (3.9) | 41 (2.1) | 71 (2.9) | 72 (3.6) | 151 (6.5) |
| ADGs | low (0-5) | 537 (36.5) | 5,112 (58.9) | 1054 (53.8) | 1426 (59.2) | 1148 (58.1) | 1453 (62.3) |
| | medium (6 – 10) | 776 (52.8) | 3,161 (36.4) | 775 (39.6) | 885 (36.7) | 686 (34.7) | 789 (33.8) |
| | high (≥11) | 158 (10.7) | 405 (4.7) | 130 (6.6) | 99 (4.1) | 78 (3.9) | 92 (3.9) |
| Income status | Q1 (poorest) | 382 (26) | 1,609 (18.5) | 355 (18.1) | 426 (17.7) | 371 (18.8) | 448 (19.2) |
| | Q2 | 296 (20.1) | 1,553 (17.9) | 365 (18.6) | 432 (17.9) | 327 (16.6) | 412 (17.7) |
| | Q3 | 224 (15.2) | 1,397 (16.1) | 323 (16.5) | 405 (16.8) | 270 (13.7) | 385 (16.5) |
| | Q4 | 223 (15.2) | 1,504 (17.3) | 322 (16.4) | 417 (17.3) | 344 (17.4) | 413 (17.7) |
| | Q5 (wealthiest) | 333 (22.6) | 2,532 (29.2) | 574 (29.3) | 710 (29.5) | 581 (29.4) | 653 (28.0) |
| ***PSG indexes*** | | | | | | | |
| TST, hours | | 5.4 (4.4-6.1) | 5.8 (5.0-6.5) | 5.9 (5.0-6.5) | 5.9 (5.1-6.5) | 5.9 (5.0-6.5) | 5.6 (4.7-6.3) |
| AHI, total in TST, events/hour | | 25.7 (11-51.7) | 14.7 (5.6-32.0) | 2.0 (0.8-3.5) | 9.3 (7.1-11.9) | 20.9 (17.7-25.1) | 48.9 (37.4-68.4) |

| **Variables** | **With diabetes** (n=1,471) | **Without diabetes** (n=8,678) | **By OSA severity for sample without diabetes** (n=8,678) | | | |
|---|---|---|---|---|---|---|
| | | | AHI<5 (n=1,959) | 5≤AHI<15 (n=2,410) | 15≤AHI≤30 (n=1,975) | AHI>30 (n=2,334) |
| AHI, total in REM, events/hour | 37.3 (14.1-59.0) | 23.5 (7.7-46.2) | 4.6 (1.4-10.2) | 20.1 (10.6-31.2) | 35.8 (20.0-50.7) | 52.8 (32.6-69.6) |
| Arousals index, total, events/hour | 30.3 (17.7-50.8) | 22.1 (13.5-36.5) | 11.4 (7.8-16.6) | 16.4 (12.1-21.8) | 25.2 (19.4-31.5) | 48.2 (35.8-64.5) |
| AWK in TST, number of events | 28 (20-41) | 24.0 (18.0-34.0) | 21.0 (15.0-27.0) | 23.0 (17.0-31.0) | 25.0 (19.0-34.0) | 32.0 (22.0-45.0) |
| TST90SaO2, minutes | 4.6 (0.3-35.6) | 0.3 (0-6.5) | 0 (0-0.1) | 0.1 (0-1.5) | 0.9 (0.0-7.2) | 10.2 (1.0-46.1) |
| Mean SaO2, % | 94.1 (92.3-95.5) | 95.0 (93.6-96.1) | 95.9 (94.8-96.8) | 95.2 (94.1-69.3) | 94.9 (93.7-95.9) | 94.0 (92.3-95.2) |
| HR, mean in TST, bpm | 65.9 (58.9-74.5) | 62.4 (56.2-69.2) | 61.8 (55.6-68.6) | 61.7 (55.5-67.9) | 62.2 (55.7-69.0) | 63.6 (57.5-70.8) |
| **Incident diabetes** | — | 1,017 (11.7) | 166 (8.5) | 253 (10.5) | 216 (10.9) | 367 (15.7) |
| **Follow-up time, months** | — | 67.2 (32.6-104.1) | 95.1 (58.4-123.7) | 71 (36.6-105) | 57.2 (28.1-94) | 48.8 (22.3-85.7) |

Ɏ Numbers may not add to total due to missing values.

*Daytime sleepiness measured by question: “During the day, do you ever fall asleep unintentionally?”
AHI - apnea hypopnea index (total and obstructive (AHIO)); ArI - total arousals index; AWK -total number of awakenings; BMI – body mass index; CABG - coronary artery bypass graft surgery; DS – daytime sleepiness; ESS – Epworth Sleepiness Scale; HR - heart rate; MI – myocardial infarction; OSA – obstructive sleep apnea; PSG- polysomnography; SaO2 - oxygen saturation; SE - sleep efficiency; TST - total sleep time; TST90SaO2 - duration of SaO2<90% in TST; Q - quintile.

**Table 2**. Model fitting and effect (HR and 95%CI) of severity of obstructive sleep apnea expressed by AHI, controlling for potential confounders and risk factors for diabetes (calculation was performed on dataset #3, n= 8678, number of events=1017).

| **OSA-related predictors** | **Model 1** | **Fully adjusted model** |
|---|---|---|
| **AHI total as a continuous variable** | | |
| AHI, total, events/hr (32 vs. 6) | 1.13 (1.06-1.20) | 1.06 (0.99-1.13) |
| LR $\chi^2$ (df )<br>$R^2$ | 754.98 (18)<br>0.10 | 841.32 (24)<br>0.11 |
| **AHI as a categorical variable (reference group: AHI<5)** | | |
| 5≤AHI<15 | 1.18 (0.97-1.44) | 1.23 (1.00-1.50) |
| 15≤AHI≤30 | 1.24 (1.01-1.53) | 1.23 (1.00-1.51) |
| AHI>30 | 1.47 (1.20-1.79) | 1.31 (1.07-1.61) |
| LR $\chi^2$ (df )<br>$R^2$ | 756.11 (20)<br>0.10 | 845.6 (26)<br>0.11 |
| Control variables | sex, age*, BMI*, history of smoking status, prior comorbidities within 3-year look-back window (HTN, MI, ADG categories) and income status | Model 1 + daytime sleepiness, neck circumference*, heart rate in sleep, and TST |

*Significantly non-linear – restricted cubic spline transformations with 4 knots were used.

Optimism for $R^2$ for all models < 0.01; Corrected C-indices ranged from 0.73 to 0.75.

ADG – aggregated diagnosis groups; AHI – apnea-hypopnea index; AMI – acute myocardial infarction; BMI – body mass index; CI – confidence interval; df – degree of freedom; DS – daytime sleepiness; HTN – hypertension; HR – hazard ratio; HTN – hypertension; LR – likelihood ratio; TST - total sleep time.

**Table 3**. Model fitting and effect (HR and 95%CI) of OSA-related predictors other than AHI, controlling for potential confounders and risk factors for diabetes (calculation was performed on dataset #3, n= 8678, number of events= 1017).

| **OSA-related predictors** | **Model 1** | **Fully adjusted model** |
|---|---|---|
| **AHI total in REM as a continuous variable** | | |
| REM-AHI, total, events/hr (46 vs. 8) | 1.22 (1.11-1.34) | 1.17 (1.07-1.29) |
| LR $\chi^2$ (df )<br>$R^2$ | 758.11 (18)<br>0.10 | 849.36 (24)<br>0.11 |
| **Sleep time spent with $SaO_2$ less than 90% as a continuous variable** | | |
| TiSaO2<90%*, min (6.4 vs. 0) | 1.06 (1.02-1.11) | 1.45 (1.20-1.76) |
| LR $\chi^2$ (df )<br>$R^2$ | 749 (19)<br>0.10 | 853.17 (26)<br>0.109 |
| Control variables | sex, age*, BMI*, history of smoking status, prior comorbidities within 3-year look-back window (HTN, AMI, ADG categories) and income status | Model 1 + daytime sleepiness, neck circumference*, heart rate in sleep time, TST |

* Significant non-linearity was observed– a restricted cubic spline transformation was used.

Optimism for $R^2$ for all models was about 0.007; Corrected C-index for all models ranged from 0.74 to 0.75.

ADG – aggregated diagnosis groups; AHI – apnea-hypopnea index; AMI – acute myocardial infarction; BMI – body mass index; CI – confidence interval; df – degree of freedom; DS – daytime sleepiness; HTN – hypertension; HR – hazard ratio; HTN – hypertension; LR – likelihood ratio; REM - rapid eye movement sleep; TST - total sleep time; TiSaO2<90% – TST with SaO2<90%.

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**Title: Obstructive Sleep Apnea and Incident Diabetes: A historical cohort study.**

**Running title:** Obstructive Sleep Apnea and Incident Diabetes

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Dr. Tetyana Kendzerska was involved in the following: literature search, study conception and design; ethics boards' application; obtaining administrative data; cleaning, analyses and interpretation of data; drafting of the manuscript.

Dr. George Tomlinson, Dr. Richard Leung, Dr. Andrea Gershon and Dr. Gillian Hawker were involved in the following: study design; data interpretation; drafting of the manuscript; critical revision; and supervision of manuscript writing.

Dr. Andrea Gershon additionally was involved in ethics boards' application, obtaining administrative data and data analyses.

Dr. George Tomlinson additionally was involved in ethics boards' application and data analyses.

Dr. Richard Leung additionally was involved in study conception, ethics boards' application, is an owner of the sleep portion of the Chest Dataset from which the study sample was extracted, and gave final approval of the submitted manuscript.

**Conflicts of interest**

All authors have indicated that they have no financial conflict of interest.

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This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

**At a Glance Commentary**

**Scientific Knowledge on the Subject:**

- Published reports on the causal relationship between OSA and incident diabetes are very limited.
- Among only six longitudinal studies published up to date, five found a significant association between obstructive sleep apnea and incident diabetes.
- However, these studies were generally small, had few events, did not account for time-to-event in their analyses, and employed inconsistent definitions of obstructive sleep apnea.
- There is a need for a larger study with rigorous assessment of both obstructive sleep apnea and diabetes, with sufficient follow-up time to allow development of disease.

**What This Study Adds to the Field:**

- Based on a large clinical cohort, our study shows that among people with obstructive sleep apnea, and controlling for known risk factors for diabetes development, initial obstructive sleep apnea severity predicted risk for incident diabetes: in fully-adjusted models, patients with apnea-hypopnea index > 30 had a 30% higher hazard of developing diabetes than those with AHI < 5.
- Apnea-hypopnea index during rapid eye movement sleep and measures of the physiologic consequences of obstructive sleep apnea (e.g., oxygen desaturation, sleep deprivation and sympathetic activation) were also risk factors for diabetes in this population.
- Risk-stratification of patients with obstructive sleep apnea according to these sleep apnea-related predictors may be useful in identifying those most likely to develop diabetes, allowing timely intervention.

**Descriptor number:** 15.7 Sleep Disordered Breathing: Epidemiology

**Words**: 3,500

## ABSTRACT

**Rationale:** Despite emerging evidence that obstructive sleep apnea (OSA) may cause metabolic disturbances independently of other known risk factors, it remains unclear whether OSA is associated with incident diabetes.

**Objective**: To evaluate whether risk of incident diabetes was related to the severity and physiological consequences of OSA.

**Methods and Measurements:** A historical cohort study was conducted using a clinical and provincial health administrative data. All adults without previous diabetes referred with suspected OSA who underwent a diagnostic sleep study at St Michael's Hospital (Toronto, Canada) between 1994 and 2010 were followed through health administrative data until May 2011 to examine the occurrence of diabetes. All OSA-related variables collected from the sleep study were examined as predictors in Cox-regression models, controlling for sex, age, body mass index, smoking status, comorbidities and income.

**Main Results**: Over a median follow-up of 67 months, 1,017 (11.7%) of 8,678 patients developed diabetes, giving a cumulative incidence at five years of 9.1% (95%CI: 8.4% to 9.8%). In fully-adjusted models, patients with apnea-hypopnea index (AHI) > 30 had a 30% higher hazard of developing diabetes than those with AHI < 5. Among other OSA-related variables, AHI in rapid eye movement (REM) sleep, and time spent with oxygen saturation less than 90% were associated with incident diabetes, as were heart rate, neck circumference and sleep time.

**Conclusions**: Among people with OSA, and controlling for multiple confounders, initial OSA severity and its physiologic consequences predicted subsequent risk for incident diabetes.

**Words**: 241


**Key words:** Sleep Apnea, Obstructive; Diabetes Mellitus; Epidemiology

## INTRODUCTION

Diabetes has been described as a public health epidemic, afflicting 10.8% of women and 11.8% of men in the United States (1). There is emerging evidence that obstructive sleep apnea (OSA), through chronic intermittent hypoxemia, recurrent arousals, and neurohumoral changes may cause metabolic disturbances including insulin resistance independently of other known risk factors (2-5) and that OSA may represent a therapeutic target in this condition (6).

It remains unclear whether OSA may lead to incident diabetes (3, 7, 8). Among six longitudinal studies, five found a significant association between OSA and incident diabetes (9-13). However, these studies were generally small, had few events, did not account for time-to-event in their analyses (9, 11, 12) and employed inconsistent definitions of OSA (e.g., apnea-hypopnea index (AHI)≥5 (9), AHI≥8 (10), oxygen desaturation index>5(12, 13)). Further, there has been very limited exploration of the prognostic value of other possibly pathophysiologically relevant OSA-related factors (e.g. arousals, total sleep time) (10). One large community-based study (the Wisconsin Sleep Cohort) reported an association between OSA and prevalent, but not incident diabetes (14). However, the number of events occurring within follow-up time was small to detect a true relationship (n=26), too many predictors for that number of events were included in analyses, and logistic regression used does not take into account the timing of the events. There is a need for a larger study with rigorous assessment of both OSA and diabetes, with sufficient follow-up time to allow development of disease. We evaluated whether risk of incident diabetes was related to the severity and physiological consequences of OSA in a large historical cohort of patients studied with in-laboratory polysomnography over more than a decade and whose health information was obtained through provincial health administrative data. Some of the results of these studies have been previously reported in the form of an abstract (15).

## METHODS

### Study Design

We included patients who were referred with suspected OSA and underwent a first diagnostic sleep study at St. Michael's Hospital (Toronto, Canada) between September 1, 1994 and December 31, 2010. Sleep laboratory clinical data were linked to health administrative data at the Institute for Clinical Evaluative Sciences (ICES, Ontario, Canada) from July 1, 1991 to March 31, 2011. The ethics committees of all institutions involved (St. Michael's Hospital, ICES, University of Toronto) approved the study. Details on cohort description are provided elsewhere (16).

### Data Sources

***Clinical data****:* The St. Michael's Hospital Sleep Lab database includes a large set of clinical, demographic and polysomnographic (PSG) variables that have been collected for research purposes since 1991 (Table E1). Each patient in the cohort underwent full in-laboratory PSG recording. Disease-specific symptoms and history were collected using standardized questionnaires.

***Health Administrative data:*** Residents of Ontario have universal public health insurance, the Ontario Health Insurance Plan (OHIP), covering all medically necessary services. All Ontario residents are eligible for OHIP coverage after 3 months of residency in the province (17). Legislation prohibits the private delivery of services covered under OHIP, including laboratory testing. Since 1991, ICES has housed high quality administrative data on publicly funded services provided, including individual-level information on physician claims, acute care hospitalization and emergency department visits within Ontario (18). The eligibility of cohort

participants for health insurance and their vital status through the follow-up period were assessed using data from the Registered Persons Database (RPDB). Administrative data regarding claims for continuous positive airway pressure (CPAP) therapy through the Ontario Assistive Devices Program (ADP) (19) have been available since 2004. A further administrative dataset used for this analysis, the Ontario Diabetes Database (ODD), was developed to establish population-based incidence and prevalence of diabetes in Ontario (20, 21). In addition to the usual ICES data from 1991, the ODD captures hospitalizations during the time period 1988-1990. Details of variables derived from administrative datasets and detail descriptions of all datasets used are provided in the online data supplement (Tables E2, E3).

**Study Sample**

Patients who had undergone a first diagnostic sleep study during the defined study period, and who had a diagnosis of OSA (AHI ≥5), or suspected OSA (referred with sleep apnea, but with AHI<5) were extracted from the St. Michael's Hospital database. Patients were excluded if they (i) underwent split-night; had (ii) more than 50% central events or (iii) AHI<5 and a diagnosis of another sleep disorder or (vi) prevalent diabetes, from the ODD, at any time between April 1988 and the diagnostic sleep study.

**Predictors**

The following variables were derived from clinical data and considered as possible predictors in our statistical models: (i) PSG indices— total sleep time (TST), AHI during TST, rapid eye movement sleep (REM-AHI), and non-REM sleep (non-REM-AHI), arousals index, total number of awakenings, mean oxygen saturation ($SaO_2$), duration of $SaO_2$<90% (TiSaO2<90%), mean heart rate (HR), and the percentage of each sleep stage; (ii) clinical symptoms— daytime sleepiness (DS), identified by mean of the Epworth Sleepiness Scale or a positive answer to the

question “During the day, do you ever fall asleep unintentionally?”; and self-reported snoring; (iii) neck circumference; (iv) self-reported family history of OSA or snoring.

The AHI was defined as the number of apneas and hypopneas per hour of sleep. Hypopnea was consistently defined during the study period as: (i) a decrease of more than 50% of the baseline amplitude of breathing for at least 10 seconds; or (ii) a clear but smaller decrease in amplitude for at least 10 seconds that is associated with either an $SaO_2$ drop of ≥3% or an arousal (22). Patients were classified as not having OSA (AHI < 5), or with mild (AHI of 5 to 14.9), moderate (AHI of 15 to 30) or severe (AHI>30) OSA (23).

**Outcome**

The primary outcome was time from the diagnostic PSG to incident diabetes derived from the ODD (20). The ODD employs a validated algorithm which identifies people with diabetes as those having at least one hospitalization record or at least two physician services claims bearing a diagnosis of diabetes within a two-year period. This algorithm is highly sensitive (86%) and specific (97%) for identifying patients in whom diabetes was recorded in primary care charts; positive predictive value is 80% (20). Use of the first service date was considered as the incident diabetes date. Subjects were followed from their first diagnostic sleep study to the end of March 2011, or the occurrence of a primary outcome or all-cause mortality, whichever occurred first.

**Potential confounders**

The following potential confounders were extracted from the Sleep Lab clinical database: age, sex, BMI, waist circumference, self-reported smoking and alcohol consumption. Comorbidities at baseline (stroke, myocardial infarction (MI), chronic heart failure (CHF), hypertension (HTN) and the Johns Hopkins’ aggregated diagnosis groups (ADGs)) were identified from administrative data over a three-year period before the diagnostic sleep study. Comorbidity at

baseline based on ADGs was categorized as low (0 to 5 ADGs), medium (6 to 10 ADGs) or high (≥11 ADGs) (24). Each patient was assigned to an income quintile using the patient's postal code.

**Statistical Analysis**

Descriptive statistics were calculated for relevant data. Crude incidence rates for diabetes per 100 person-years were calculated for the entire sample and by OSA severity (23, 25). In a frail population, death, termed a competing event, may preclude the occurrence of diabetes and lead to overestimation of incidence by the usual Kaplan-Meier method (26). Therefore, we estimated incidence with the cumulative incidence function, which accounts for competing risks. Formal tests for differences in incident diabetes and all-cause mortality between groups were performed using the modified $\chi^2$ statistic (27).

We used multivariable Cox regression models to investigate the relationships between OSA-related predictors and incident diabetes, and expressed the results as hazard ratios (HRs) (28, 29) (more details in the online data supplement). AHI was treated as both a continuous and categorical variable. We used restricted cubic spline (28) transformations for continuous explanatory variables if non-linearity was observed, and the resulting standardized HRs compare the 75th and 25th percentiles. To confirm findings from traditional multivariable Cox-regression model, the Fine and Gray competing-risk regression model was used (30).

For missing variables we used multivariate imputation by chained equations to generate five complete datasets (31) and pooled the coefficients (32). For a unified presentation of all results and figures, the findings shown are for a single imputed dataset. Pooled CIs across imputations for OSA-related variables were at most 2% wider than those presented.

Systematic reviews (8, 33) and expert opinion found age, sex, smoking status, CV comorbidities, BMI, AHI, TST and DS to be important for predicting diabetes, so these variables were forced into the models. Although waist circumference is a more accurate measure of obesity than BMI, BMI was chosen to be included in our statistical model as it improved model fit compared to waist circumference and is easier to obtain in routine clinical practice and less affected by measurement error. Other variables were chosen for inclusion if they were selected by backward step-down variable deletion (34) in at least three imputed datasets. We investigated a priori - defined interactions between AHI and DS, BMI, age, sex and CVD at baseline (8).

We used the bootstrap for internal validation and over-fitting-corrected calibration. Discriminative ability was assessed using Harrell's C-index and predictive ability using the model likelihood ratio $\chi^2$ statistic (28).

To address the concern that the exact time of the incident diabetes is unknown, we used a binomial regression with the complementary log-log link function, which allows incorporation of different follow-up time for each subject in the model to estimate incidence rate ratio (35, 36).

***Sensitivity analysis***. In the post-2004 cohort with information on CPAP claims, the final model was refitted with the addition of a time-dependent CPAP treatment variable (more details in the online data supplement, Figure E1). To assess the effect of OSA-related predictors on an untreated sample, patients were censored at the time of a CPAP claim.

Additional sensitivity analyses included the following: analyses in which only participants who were eligible for OHIP all of each year (i.e., not out of the province during the year) with at least 5 years look-back window and at least 2 years follow-up; all gave the similar results with the main analyses (data not shown). Finally, the statistical models were refitted on the entire sample including participants who underwent split-night study (Table E6).

Finally, to assess the sensitivity of results to unmeasured confounders, we used the approach recommended by Lin et al, 1998 (37).

Additional details on the method are provided in the online data supplement.

All statistical analyses were performed using R version 2.15.2 (http://www.r-project.org) and SAS 9.3.

***Sample size consideration***. We expected between 162 and 1,038 events based on an anticipated sample of 5000 persons with an average of 5 years of follow-up and reported rates of incident diabetes from 0.65 to 4.15 per 100 person-years (9-12, 14). That would allow us to examine at least 16 predictors, using the rule of thumb of 10 events per predictor (38).

## RESULTS

### Sample Characteristics

Between January 1, 1994 and December 31, 2010, 11,596 individuals underwent a first diagnostic sleep study and 10,149 (88%) were linked to administrative datasets (Figure E2). Patients who were not linked had similar OSA severity and demographic characteristics, but fewer CV comorbidities and greater daytime sleepiness (16). Our final analyses included 8,678 participants without diabetes at baseline. Table 1 shows baseline characteristics of patients for the entire sample and by OSA severity. The included sample had 62% males, a median age of 48 years and a median AHI of 15. The amount of missing data ranged from 0.7% (AHI) to10.1% (TiSaO2<90%), 2.4% was missed for BMI and TST, 6.8% - for daytime sleepiness, 7.8% - for heart rate, and 8.2% - for smoking status (16).

### Incidence of diabetes

Over a median follow-up of 67 months, 1,017 (11.7%) participants experienced incident diabetes, giving an incidence rate of 2 per 100 person-years. The potential competing event, death without diagnosed diabetes, occurred in 395 subjects. Cumulative incidence of diabetes at five years for the entire sample was 9.1% (95%CI: 8.4%-9.8%); for patients with mild OSA – 7.5% (6.3%-8.6%), with moderate OSA – 9.9% (8.3%-11.4%), with severe OSA – 14.9% (13.2%-16.6%). The unadjusted difference in incidence of diabetes was significant ($p<0.0001$) between patients with severe OSA and AHI<5.

**Multivariable Cox Regression Models**

Table 2 shows the HR estimates and model fit statistics for the two classes of models we examined, with AHI as a continuous or categorical variable. In fully-adjusted model, severe OSA as defined by AHI was significantly associated with incident diabetes. Patients with severe OSA had a 30% higher hazard of developing diabetes compared to those without OSA, while mild and moderate OSA had a 23% higher hazard (Table 2, Figure 1). Among other OSA-related predictors, REM-AHI, and TiSaO2<90% were consistently associated with incident diabetes (Table 3), as were daytime sleepiness, heart rate in sleep, neck circumference and sleep time (Figure 1, Table E5). All models were well calibrated (all observed and predicted five-year survival within 2%) and validated (optimism for $R^2$ for all explored models was ≤0.007).

**Competing risk analyses**

In the Fine and Gray regression, the effects of DS, neck circumference, heart rate, and OSA severity on incident diabetes had similar HRs to those from the Cox regression and remained significant, while the effect of sleep time became non-significant.

**Interactions**

The effect of AHI on incident diabetes significantly decreased with increased BMI (p=0.0013) and age (p=0.0326) (Table E5).

**CPAP treatment effect**

Among 3,931 subjects who underwent a diagnostic PSG between 2004 and 2010, 611 (15.5%) submitted a CPAP claim. Among 267 (6.8%) patients who experienced incident diabetes, 66 claimed CPAP before the incident date (24.7%), and 7 after (2.6%); among the other 3,664 subjects, 538 (14.7%) claimed for CPAP treatment. A claim for CPAP treatment had a non-significant effect in fully-adjusted models on the risk of diabetes (p values > 0.2). When models were refitted on an untreated sample, all predictors except DS remained significantly associated with the outcome.

**Complementary log-log regression model**

After accounting for follow-up time in the binomial regression model, AHI, REM-AHI and TiSaO2<90% remained significant, as did sleep time, DS, heart rate, and neck circumference.

**DISCUSSION**

In a large clinical cohort without diabetes at baseline, 11.7% of subjects experienced incident diabetes over a median 67 months of follow-up. The multivariable Cox regression models identified that OSA severity, expressed as AHI, was independently and significantly associated with incident diabetes. In addition, the OSA-related factors REM-AHI and TiSaO2<90% were significant predictors, as were shorter total sleep time, higher mean heart rate, greater neck circumference and the presence of daytime sleepiness. In an untreated subsample, all predictors except DS remained significantly associated with the outcome. The effects of predictors were consistent in a model adjusting for the competing risk of all-cause mortality and in a binomial

regression accounting for imprecision in the date of diagnosis of diabetes. The present study agrees with the much smaller single study that looked at time-to-diagnosis of diabetes by Botros et al (2009), which found an independent association between OSA and incident diabetes after adjusting for multiple confounding factors (10).

Our study addresses limitations of previously published observational studies of OSA and diabetes. Due to its larger size (more than 8,500 patients) and longer period of complete follow-up (more than 10 years), our study was able to analyze a number of events that is more than an order of magnitude larger than occurred in any previous study, including the Wisconsin Cohort Study. Further, this allowed assessment of many OSA-related factors beyond AHI and adequate control for numerous potential confounders impossible in a smaller study. Clinical data were consistently collected and used the same PSG scoring criteria over time. We included patients with a wider range of OSA severity than observed in community-based studies and a relatively large number of females. We used validated algorithms to define prevalent diabetes and comorbidities at baseline, and, finally, used rigorous methods for missing data, model selection, calibration and validation.

Our findings (that longer TiSaO2<90%, shorter sleep time and higher heart rate increase the risk of diabetes) are consistent with proposed pathophysiological mechanisms (oxidative stress caused by intermittent hypoxemia, sleep deprivation or sleep fragmentation, and sympathetic activation) whereby OSA may lead to diabetes. Severity of hypoxemia has been found to be associated with glucose intolerance and insulin resistance (39, 40). Sleep deprivation may act through sympathetic activation and subsequent alterations in hypothalamic-pituitary-adrenal axis (4, 41). Elevated resting heart rate, an indicator of sympathetic nerve activity, has

been shown to be associated with incident diabetes through possible relation between sympathetic activity and insulin resistance (42, 43).

Similarly, neck circumference, a strong clinical predictor of OSA (44) and a significant independent predictor of incident diabetes in our study, has also been associated with impaired glucose homeostasis and cardio-metabolic syndrome (45, 46).

We found that in addition to overall AHI during TST, REM–AHI was also an independent predictor of diabetes. Compared with NREM sleep, REM sleep has been shown to be associated with greater sympathetic activity and respiratory and cardiovascular instability. Apneas during REM sleep lead to greater degrees of hypoxemia and sympathetic activity compared with events in NREM sleep (47). In a cross-sectional study on a predominantly African American and Hispanic cohort, REM-AHI, but not overall AHI, was significantly and independently associated with diabetes (48). Similarly, we found that REM-AHI was significantly associated with incident diabetes and had a larger effect than overall AHI. The clinical importance of AHI in REM may have significant implications for clinical practice (47).

The decreased effect of AHI with age on incident diabetes found in our study has been observed previously for the relationship between OSA and mortality (49). Protective adaptive physiological change through longstanding mild chronic intermittent hypoxia is one of the possible explanations (50). A similar effect on the association between AHI and incident diabetes was found for BMI: the effect of AHI decreased with increasing BMI. It is possible that very obese individuals are already at such high risk for developing diabetes that OSA confers little incremental risk.

There are several limitations that should be considered in the interpretation of our findings. As with any observational study, some methodological issues are related to availability

of data. Some important confounders (e.g., family history of diabetes, race) were not available. The generalizability can be affected by the single center design of our study. Also using the ODD to derive incident diabetes, we were unable to distinguish between Type 1 and Type 2 diabetes. However, we expect the vast majority of events to be Type 2 because of the age of our cohort. Though validated algorithms were used to define prevalent diabetes and prior comorbidities from health administrative data, these algorithms are characterized by certain sensitivity and specificity resulting in possible misclassification of subjects. If differential, bias could go in either direction, while if non-differential (misclassified randomly and independently of disease state), the estimated effect of OSA severity on incident diabetes is more likely to fall below the true value (51, 52). Because of universal health care in Ontario, this measurement error (undiagnosed cases of diabetes in the cohort) was likely independent of the exposure (severe OSA), so we may have underestimated the true effects. With respect to defining incident diabetes cases using the ODD, a small proportion of prevalent cases may be misclassified as incident cases. This may occur when disease was not captured in the administrative health data within observational period prior to baseline for patients with true diabetes. In addition, the date of diagnosed diabetes in administrative data is not the exact time of diabetes development: it could have occurred any time before this date. Using the complementary log-log link regression we tried to address this limitation and have not revealed any important differences compared to the Cox-regression model. Finally, patients with more severe OSA may have more contact with the health care system and may be more likely to be tested for diabetes and consequently diagnosed with diabetes. We addressed this issue by adjusting our models for age, sex, BMI and baseline comorbidities, known predictors of health care utilization for OSA patients (53). Among variables tested in our models, older age, hypertension, and higher income have been also shown

to be associated with a higher likelihood of having a glucose test (54). Further, we assessed the sensitivity of the results to unmeasured confounders and found that only fairly strong confounding reduced the HR of 1.31 sufficiently, that it was no longer statistically significant (details are provided in the online data supplement, Table E4, Figure E3). In particular, the odds ratio between the confounder and OSA severity needed to be 2.5 to 3. Although an unmeasured confounder could be any unmeasured feature of the patient, we were most concerned about screening for diabetes. Since it is implausible that screening occurs 2.5 to 3 times more often in those with AHI > 30 compared to those with AHI < 5, when we have already accounted for age, sex, prior comorbidities and income status, we believe that confounding by diabetes screening is not solely responsible for the observed HR of 1.31. The true HR may be lower than 1.31, but remains statistically significantly elevated for reasonable assumptions about unmeasured confounding.

The non-significant effect of treatment that we found in the post-2004 cohort could be explained by lack of information about CPAP adherence, treatment approaches other than CPAP, and reduced sample size for this analysis. Also, patients would have been suffering from physiological consequences of OSA for many years before starting treatment that could have increased their risk of developing adverse long-term consequences. Nevertheless, since a treatment effect may attenuate a possible association between OSA and incident diabetes, we conducted an additional analysis on untreated subsample only. This subsample analysis replicates the results obtained on the entire cohort. Thus, the non-significant association between CPAP claims and the outcome of interest should not be interpreted as a lack of efficacy of CPAP treatment in preventing diabetes as our study was not designed to address this question.

Our study shows that among people with OSA, and controlling for multiple confounders, initial OSA severity predicted risk for incident diabetes. AHI during REM sleep and measures of the physiologic consequences of OSA (e.g., oxygen desaturation, sleep deprivation and sympathetic activation) were also risk factors for diabetes in this population. Risk-stratification of patients with OSA according to these OSA parameters may be useful in identifying those most likely to develop diabetes, allowing timely intervention.

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**Figure legends.**

**Figure 1.** Results from multivariable Cox regression model presented as standardized hazard ratios (comparing 75$^{th}$ percentile to 25$^{th}$ percentile) with shading representing confidence levels (99%, 95%, 90%, 80% and 70%).

ADG – comorbidity defined using aggregated diagnostic groups as low (1), medium (2) or high (3); AHI – apnea-hypopnea index, events/hour; AMI – acute myocardial infarction; BMI – body mass index, kg/m$^2$; daytime sleepiness – identified by a positive answer to the question "During the day, do you ever fall asleep unintentionally?"; HR – heart rate, bpm; income - income quintiles, ranked from poorest (1) to wealthiest (5); NECK – neck circumference, cm; TST – total sleep time, hours.

**Table 1**. Characteristics of patient with a full-night diagnostic sleep study who were linked to the health administrative data: without diabetes at baseline (n=8,678) and with diabetes at baseline (n =1,471)). Median (interquartile range, IQR) or n (%)¥.

| **Variables** | | **With diabetes** (n=1,471) | **Without diabetes** (n=8,678) | **By OSA severity for sample without diabetes** (n=8,678) | | | |
|---|---|---|---|---|---|---|---|
| | | | | AHI<5 (n=1,959) | 5≤AHI<15 (n=2,410) | 15≤AHI≤30 (n=1,975) | AHI>30 (n=2,334) |
| ***Demographic characteristics*** | | | | | | | |
| Male | | 909 (61.8) | 5,377 (62) | 893 (45.6) | 1399 (55.6) | 1238 (62.7) | 1808 (77.5) |
| Age, years | | 59.0 (50.0-68.0) | 48.0 (38.0-58.0) | 42.0 (33.0-51.0) | 47.0 (38.0-57.0) | 50.0 (41.0-59.0) | 51.0 (43.0-61.0) |
| ***Clinical symptoms and findings from physical examination*** | | | | | | | |
| DS*, Yes | | 663 (45.1) | 2,994 (34.5) | 629 (32.1) | 754 (31.3) | 614 (31.1) | 966 (41.4) |
| ESS total (0-24) | | 8.0 (5.0-12.0) | 8.0 (5.0-12) | 8.0 (5.0-12.0) | 8.0 (4.0-12.0) | 8.0 (5.0-12.0) | 8.0 (5.0-12.0) |
| BMI, kg/m$^2$ | | 32.0 (28.1-37.6) | 28.4 (25.1-32.7) | 25.8 (22.9-29.6) | 27.8 (24.8-31.5) | 28.8 (25.7-32.8) | 31.1 (27.5-35.7) |
| Neck circumference, cm | | 41.0 (38.0-44.0) | 39.0 (36.0-42.0) | 37.0 (33.0-39.0) | 38.0 (36.0-41.0) | 40 (37.0-42.0) | 41.0 (39.0-44.0) |
| ***History*** | | | | | | | |
| Smoking status, self-reported | current | 193 (13.1) | 1,646 (19.0) | 377 (19.2) | 476 (19.8) | 342 (17.3) | 435 (18.6) |
| | ex-smoker | 351 (23.9) | 1,518 (17.5) | 263 (13.4) | 373 (15.5) | 362 (18.3) | 501 (21.5) |
| | never | 761 (51.7) | 4,845 (55.8) | 1181 (60.3) | 1354 (56.2) | 1075 (54.4) | 1207 (51.7) |
| Prior HTN | | 1,004 (68.3) | 2,638 (30.4) | 340 (17.4) | 611 (25.4) | 652 (33.0) | 1019 (43.7) |
| Prior AMI | | 159 (10.8) | 241 (2.8) | 26 (1.3) | 50 (2.1) | 58 (2.9) | 106 (4.5) |
| Prior Stroke | | 77 (5.2) | 146 (1.7) | 16 (0.8) | 46 (1.9) | 27 (1.4) | 56 (2.4) |
| Prior CHF | | 282 (19.2) | 336 (3.9) | 41 (2.1) | 71 (2.9) | 72 (3.6) | 151 (6.5) |
| ADGs | low (0-5) | 537 (36.5) | 5,112 (58.9) | 1054 (53.8) | 1426 (59.2) | 1148 (58.1) | 1453 (62.3) |
| | medium (6 – 10) | 776 (52.8) | 3,161 (36.4) | 775 (39.6) | 885 (36.7) | 686 (34.7) | 789 (33.8) |
| | high (≥11) | 158 (10.7) | 405 (4.7) | 130 (6.6) | 99 (4.1) | 78 (3.9) | 92 (3.9) |
| Income status | Q1 (poorest) | 382 (26) | 1,609 (18.5) | 355 (18.1) | 426 (17.7) | 371 (18.8) | 448 (19.2) |
| | Q2 | 296 (20.1) | 1,553 (17.9) | 365 (18.6) | 432 (17.9) | 327 (16.6) | 412 (17.7) |
| | Q3 | 224 (15.2) | 1,397 (16.1) | 323 (16.5) | 405 (16.8) | 270 (13.7) | 385 (16.5) |
| | Q4 | 223 (15.2) | 1,504 (17.3) | 322 (16.4) | 417 (17.3) | 344 (17.4) | 413 (17.7) |
| | Q5 (wealthiest) | 333 (22.6) | 2,532 (29.2) | 574 (29.3) | 710 (29.5) | 581 (29.4) | 653 (28.0) |
| ***PSG indexes*** | | | | | | | |
| TST, hours | | 5.4 (4.4-6.1) | 5.8 (5.0-6.5) | 5.9 (5.0-6.5) | 5.9 (5.1-6.5) | 5.9 (5.0-6.5) | 5.6 (4.7-6.3) |
| AHI, total in TST, events/hour | | 25.7 (11-51.7) | 14.7 (5.6-32.0) | 2.0 (0.8-3.5) | 9.3 (7.1-11.9) | 20.9 (17.7-25.1) | 48.9 (37.4-68.4) |

| **Variables** | **With diabetes** (n=1,471) | **Without diabetes** (n=8,678) | **By OSA severity for sample without diabetes** (n=8,678) | | | |
|---|---|---|---|---|---|---|
| | | | AHI<5 (n=1,959) | 5≤AHI<15 (n=2,410) | 15≤AHI≤30 (n=1,975) | AHI>30 (n=2,334) |
| AHI, total in REM, events/hour | 37.3 (14.1-59.0) | 23.5 (7.7-46.2) | 4.6 (1.4-10.2) | 20.1 (10.6-31.2) | 35.8 (20.0-50.7) | 52.8 (32.6-69.6) |
| Arousals index, total, events/hour | 30.3 (17.7-50.8) | 22.1 (13.5-36.5) | 11.4 (7.8-16.6) | 16.4 (12.1-21.8) | 25.2 (19.4-31.5) | 48.2 (35.8-64.5) |
| AWK in TST, number of events | 28 (20-41) | 24.0 (18.0-34.0) | 21.0 (15.0-27.0) | 23.0 (17.0-31.0) | 25.0 (19.0-34.0) | 32.0 (22.0-45.0) |
| TST90SaO2, minutes | 4.6 (0.3-35.6) | 0.3 (0-6.5) | 0 (0-0.1) | 0.1 (0-1.5) | 0.9 (0.0-7.2) | 10.2 (1.0-46.1) |
| Mean SaO2, % | 94.1 (92.3-95.5) | 95.0 (93.6-96.1) | 95.9 (94.8-96.8) | 95.2 (94.1-69.3) | 94.9 (93.7-95.9) | 94.0 (92.3-95.2) |
| HR, mean in TST, bpm | 65.9 (58.9-74.5) | 62.4 (56.2-69.2) | 61.8 (55.6-68.6) | 61.7 (55.5-67.9) | 62.2 (55.7-69.0) | 63.6 (57.5-70.8) |
| **Incident diabetes** | — | 1,017 (11.7) | 166 (8.5) | 253 (10.5) | 216 (10.9) | 367 (15.7) |
| **Follow-up time, months** | — | 67.2 (32.6-104.1) | 95.1 (58.4-123.7) | 71 (36.6-105) | 57.2 (28.1-94) | 48.8 (22.3-85.7) |

Ɏ Numbers may not add to total due to missing values.

*Daytime sleepiness measured by question: “During the day, do you ever fall asleep unintentionally?”
AHI - apnea hypopnea index (total and obstructive (AHIO)); ArI - total arousals index; AWK -total number of awakenings; BMI – body mass index; CABG - coronary artery bypass graft surgery; DS – daytime sleepiness; ESS – Epworth Sleepiness Scale; HR - heart rate; MI – myocardial infarction; OSA – obstructive sleep apnea; PSG- polysomnography; SaO2 - oxygen saturation; SE - sleep efficiency; TST - total sleep time; TST90SaO2 - duration of SaO2<90% in TST; Q - quintile.

**Table 2**. Model fitting and effect (HR and 95%CI) of severity of obstructive sleep apnea expressed by AHI, controlling for potential confounders and risk factors for diabetes (calculation was performed on dataset #3, n= 8678, number of events=1017).

| **OSA-related predictors** | **Model 1** | **Fully adjusted model** |
|---|---|---|
| **AHI total as a continuous variable** | | |
| AHI, total, events/hr (32 vs. 6) | 1.13 (1.06-1.20) | 1.06 (0.99-1.13) |
| LR $\chi^2$ (df )<br>$R^2$ | 754.98 (18)<br>0.10 | 841.32 (24)<br>0.11 |
| **AHI as a categorical variable (reference group: AHI<5)** | | |
| 5≤AHI<15 | 1.18 (0.97-1.44) | 1.23 (1.00-1.50) |
| 15≤AHI≤30 | 1.24 (1.01-1.53) | 1.23 (1.00-1.51) |
| AHI>30 | 1.47 (1.20-1.79) | 1.31 (1.07-1.61) |
| LR $\chi^2$ (df )<br>$R^2$ | 756.11 (20)<br>0.10 | 845.6 (26)<br>0.11 |
| Control variables | sex, age*, BMI*, history of smoking status, prior comorbidities within 3-year look-back window (HTN, MI, ADG categories) and income status | Model 1 + daytime sleepiness, neck circumference*, heart rate in sleep, and TST |

*Significantly non-linear – restricted cubic spline transformations with 4 knots were used.

Optimism for $R^2$ for all models < 0.01; Corrected C-indices ranged from 0.73 to 0.75.

ADG – aggregated diagnosis groups; AHI – apnea-hypopnea index; AMI – acute myocardial infarction; BMI – body mass index; CI – confidence interval; df – degree of freedom; DS – daytime sleepiness; HTN – hypertension; HR – hazard ratio; HTN – hypertension; LR – likelihood ratio; TST - total sleep time.

**Table 3**. Model fitting and effect (HR and 95%CI) of OSA-related predictors other than AHI, controlling for potential confounders and risk factors for diabetes (calculation was performed on dataset #3, n= 8678, number of events= 1017).

| **OSA-related predictors** | **Model 1** | **Fully adjusted model** |
|---|---|---|
| **AHI total in REM as a continuous variable** | | |
| REM-AHI, total, events/hr (46 vs. 8) | 1.22 (1.11-1.34) | 1.17 (1.07-1.29) |
| LR $\chi^2$ (df )<br>$R^2$ | 758.11 (18)<br>0.10 | 849.36 (24)<br>0.11 |
| **Sleep time spent with $SaO_2$ less than 90% as a continuous variable** | | |
| TiSaO2<90%*, min (6.4 vs. 0) | 1.06 (1.02-1.11) | 1.45 (1.20-1.76) |
| LR $\chi^2$ (df )<br>$R^2$ | 749 (19)<br>0.10 | 853.17 (26)<br>0.109 |
| Control variables | sex, age*, BMI*, history of smoking status, prior comorbidities within 3-year look-back window (HTN, AMI, ADG categories) and income status | Model 1 + daytime sleepiness, neck circumference*, heart rate in sleep time, TST |

* Significant non-linearity was observed– a restricted cubic spline transformation was used.

Optimism for $R^2$ for all models was about 0.007; Corrected C-index for all models ranged from 0.74 to 0.75.

ADG – aggregated diagnosis groups; AHI – apnea-hypopnea index; AMI – acute myocardial infarction; BMI – body mass index; CI – confidence interval; df – degree of freedom; DS – daytime sleepiness; HTN – hypertension; HR – hazard ratio; HTN – hypertension; LR – likelihood ratio; REM - rapid eye movement sleep; TST - total sleep time; TiSaO2<90% – TST with SaO2<90%.

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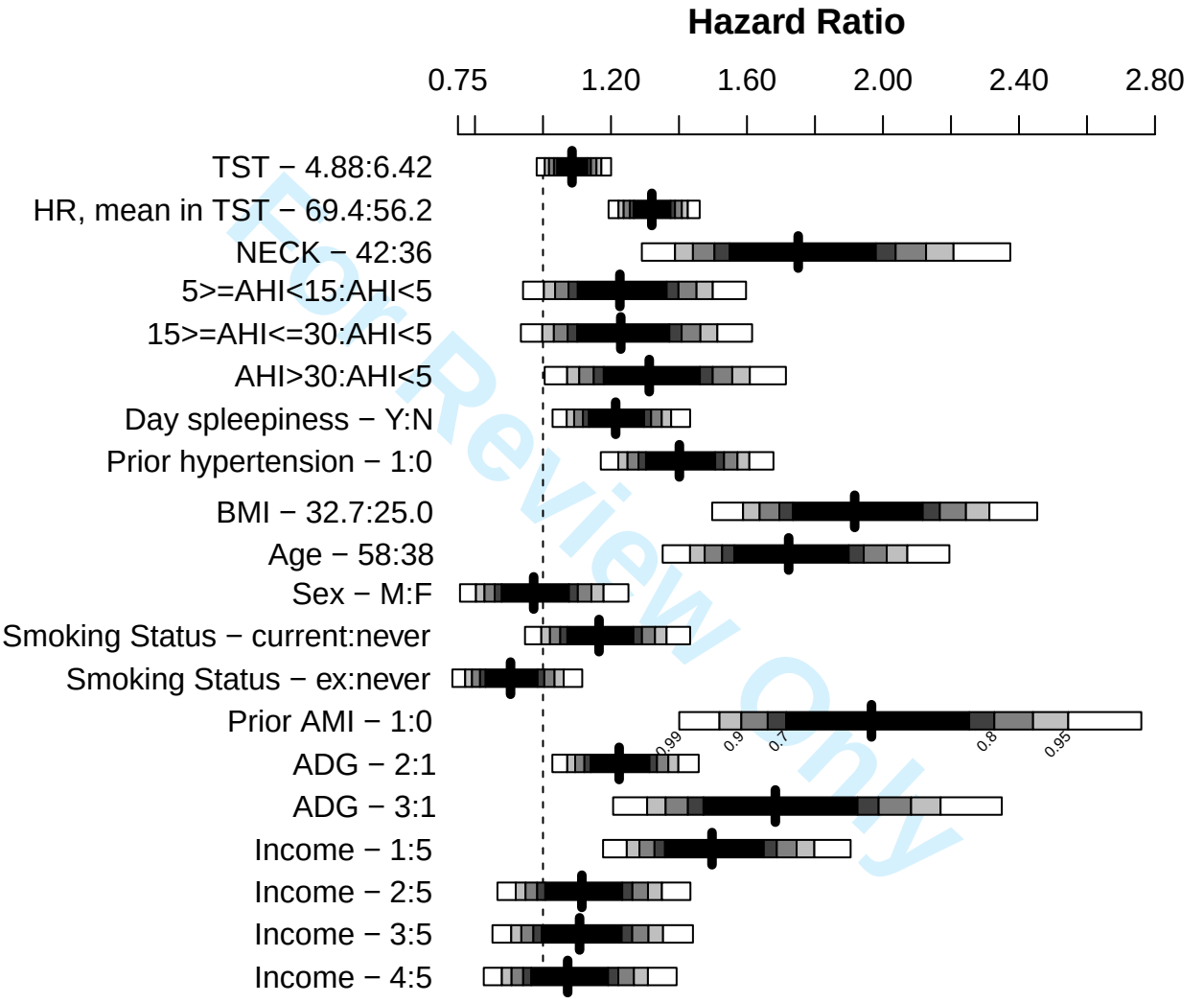

**Online Data Supplement**

**Title: Obstructive Sleep Apnea and Incident Diabetes: A historical cohort study.**
**Authors:** Tetyana Kendzerska, Andrea S. Gershon, Gillian Hawker, George Tomlinson, Richard S. Leung

## Table of Contents

**Method: Model diagnostics**

We considered the following types of model diagnostics: (i) testing violation of the assumption of proportional hazards and identification of influential observations (distributional); (ii) testing nonlinearity in the relationship between the log hazard ratio and the covariates (linearity); and (iii) evaluating if the effect of each independent variable is completely separate from the other independent variables (additive effects, i.e. no interaction) (1).

The Cox proportional hazards regression assumptions for each variable were tested using a graphical approach (visually examining distribution of Schoenfeld residuals), and analytical method (a global test of the proportional hazards) (2, 3). The assumption is that the hazard ratio for each variable is constant over time: if the proportional hazard assumption for a parameter is true, then a plot of residuals (r) for this parameter versus time should lie around a horizontal line (in a linear regression model: $E(r)=\alpha+\beta*time$, and beta = 0 if the proportional hazard assumption is true) (2). The global test also uses the scaled Schoenfeld residuals (3). If beta is significantly different from zero, then the proportional hazards assumption was rejected.

An observation was defined as influential if removing the observation substantially changes the predicted scores for other observations. DFBETAS were used to measure the difference between the parameter estimate with a particular observation included and the estimate without that particular observation, divided by the standard error of the parameter from the full dataset; a cut-off of 0.2 was used to identify influential observations (4, 5). Only for 15 participants was at least one influential value was found; given the sample size of about 10,000, we decided to keep the influential observations in dataset.

To address a concern that predictors may be strongly correlated with each other, collinearity was assessed using "variance inflation factors" (VIF) approach (6). VIFs measure the degree to which collinearity among the predictors degrades the precision of estimated coefficients. An increase in the standard errors of the regression coefficient estimates reduces the power of the corresponding tests. VIFs were computed from the covariance matrix of parameter estimates (7). VIF>10 were considered as indicators of collinearity (8). In our models values of VIFs were all smaller than 3, indicating minimal problems associated with multicollinearity.

To detect nonlinearity, the relationship between each predictor and the log relative hazard of incident diabetes as well as the martingale residuals against covariates were plotted. Wald statistics were used to quantify non-linearity of each predictor in a model with all continuous variables transformed (4). We used restricted cubic spline transformations with 4 knots for continuous explanatory variables if non-linearity was observed. This spline function is a smoothly-joined piecewise polynomial (2). Endpoints of the intervals are called knots. Knots reflect fixed quantiles of predictor's marginal distribution; we used the $5^{th}$, $35^{th}$, $65^{th}$ and $95^{th}$ percentiles when we used 4 knots.(2) Cubic splines have been frequently recommended use because they provide flexibility for fitting data, are visually smooth, and constrained to be linear in the tails where there is less data to estimate a smooth function (9).

To test additivity, we investigated a priori-defined interactions between AHI or $SaO_2$ and DS, BMI, age, sex and CVD at baseline (10). Visual and quantitative approaches were used to investigate the effect of modifiers. The relationship between AHI or $SaO_2$ and the log hazard ratio were plotted separately by different subgroups (e.g., male vs. females; reported DS vs. not). Main effects model were compared to full models with interactions using the likelihood ratio tests (2).

**Sensitivity analysis: Treatment for OSA patients**

Since CPAP treatment is the recommended first line treatment for OSA (11), it was important to include information about CPAP treatment and compliance in our statistical model. However, this information was not available in the clinical data. Therefore, we developed an algorithm to identify the use of CPAP treatment from health administrative data: patients were considered as treated from the time of the CPAP claim in the Assistive Devices Program (ADP) dataset (Figure E1). As the ADP dataset covers the years only since 2004, the effect of treatment was assessed in a cohort restricted to patients having a sleep study between 2004 and 2010.

In Ontario, the Ministry of Health and Long-Term Care, Assistive Devices Program (ADP) pays for CPAP systems for people who have been diagnosed by a sleep physician as having obstructive sleep apnea syndrome (http://www.health.gov.on.ca/en/public/programs/adp/publications/cpap.aspx). The ADP pays 75% of the ADP approved price or maximum of $780. For those patients who are receiving social assistance benefits from Ontario Works, Ontario Disability Support Program, ADP may pay 100% of the ADP approved price.

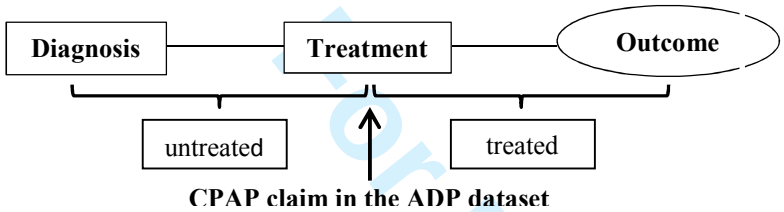


**Figure E1**. CPAP treatment effect: patients were considered as treated from the time of the claim in the ADP dataset

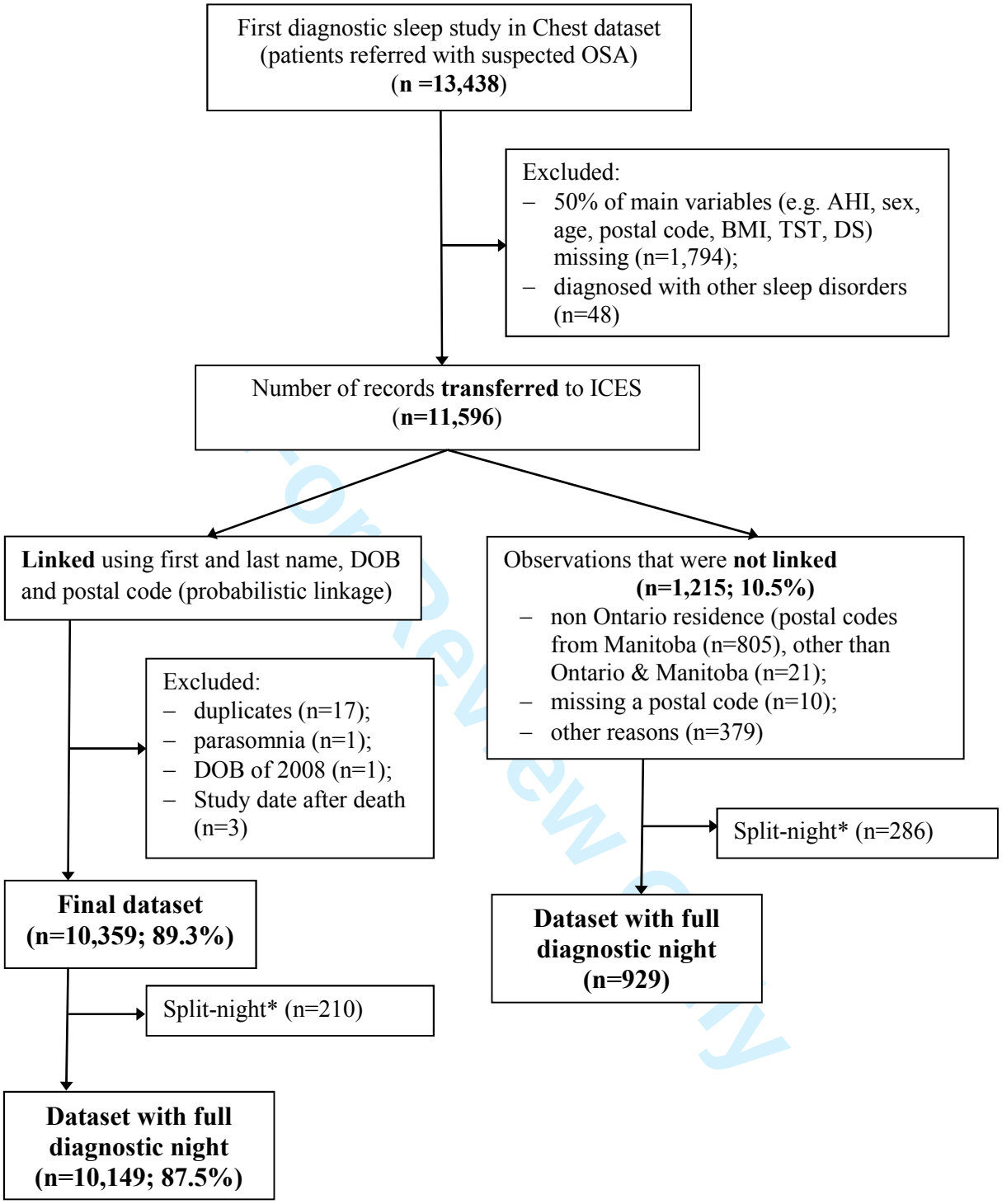


**Figure E2.** Flow diagram of the final cohort

AHI – apnea-hypopnea index, BMI – body mass index, DS – daytime sleepiness, TST – total sleep time.
*Split night – diagnostic study night when treatment was initiated due to severe OSA.

**Table E1. List of variables collected in the sleep laboratory** (each patient in the cohort underwent an overnight full standard PSG recording which was scored manually by a sleep technologist and reviewed by a board-certified sleep physician).

| Name | Description | Measurement |
|---|---|---|
| ***Demographic characteristics (self-reported by patients)*** | | |
| Sex | | Male/Female |
| Age | | years |
| ***Symptoms related to OSA (self-reported by patients)*** | | |
| *Daytime sleepiness* | | |
| Epworth Sleepiness Scale, total | Total score | ranged from 0 to 24 |
| Item #1 | Sitting and reading | 0 = would never doze<br>1 = slight chance of dozing<br>2 = moderate chance of dozing<br>3 = high chance of dozing |
| Item #2 | Watching TV | from 0 to 3 |
| Item #3 | Sitting inactive in a public place (e.g. a theatre or at a meeting) | from 0 to 3 |
| Item #4 | As a passenger in a car for an hour without a break | from 0 to 3 |
| Item #5 | Lying down in the afternoon when circumstances permit | from 0 to 3 |
| Item #6 | Sitting and talking to someone | from 0 to 3 |
| Item #7 | Sitting quietly after a lunch without alcohol | from 0 to 3 |
| Item #8 | In a car while stopped for a few minutes in traffic | from 0 to 3 |
| Self-reported DS | "During the day, do you ever fall asleep unintentionally?" | Yes/No |
| *Other symptoms (self-reported by patients)* | | |
| Snoring | Do you snore? | Yes/No |
| Observed cessation of breathing | Has anyone ever told you that you stop breathing while you sleep? | Yes/No |
| Observed restless sleeper | Have you been told that you are a restless sleeper? | Yes/No |
| Wake unrefreshed | Do you feel refreshed when you wake up? | Yes/No |
| Morning headache | Do you often wake up with headaches in the morning? | Yes/No |
| ***History (self-reported by patients)*** | | |
| Smoking status | | current<br>ex-smoker<br>never |
| Alcohol consumption* | "Y" > 7 alcoholic beverages per week, other - "N" | Yes/No |
| High blood pressure | Do you, or have you ever suffered from high blood pressure? | Yes/No |
| Myocardial Infarction | Self-reported myocardial infarction | Yes/No |
| Stroke | Self-reported stroke | Yes/No |
| History of Family Snore | Does anybody else in your family snore loudly? | Yes/No |
| History of Family Apnea Diagnosis | Has anyone in your family been diagnosed with sleep apnea? | Yes/No |
| ***Physical examination by sleep technician according to the lab manual*** | | |
| SBP* | Systolic blood pressure (SBP), measured in the evening (pm) | mm Hg |
| DBP* | Diastolic blood pressure, measured in the evening (pm) | mm Hg |
| WGT | weight | kg |
| HGT | height | cm |
| NECK | neck circumference | cm |
| WAIST | waist circumference | cm |
| HIP | hip circumference | cm |
| ***PSG recording: PSG software used is different version of Sandman (current - 7.3)*** | | |
| TST | Time in Bed (TIB) – Sleep Latency (SL) | total sleep time, hours |
| Sleep efficiency | TST/TIB | % |
| STAGE1 | The PSG was scored manually for sleep stage according to established criteria using the EEC, EOG and EMG records (12). | % of stage 1 |
| STAGE2 | | % of stage 2 |
| STAGE3 | | % of stage 3 |
| STAGE4 | | % of stage 4 |
| REM sleep | | % of rapid eye movement sleep |
| Heart rate in TST | Overall mean heart rate in TST | bpm |
| PLMI in TST | The number of periodic leg movements per hour of TST | events/hr. |
| ArI, total | Total Arousals index in TST | events/hr. |
| AWK in TST | Total Awakenings, number in TST | events/TST |
| Mean of $SaO_2$ in TST | Overall Mean $SaO_2$% in TST | % |

| | | |
|---|---|---|
| $TiSaO_2$<90% | Duration of $SaO_2$<90% in TST | minutes |
| | % of $SaO_2$<90%, in TST | % |
| *Apnea and hypopnea events* | | |
| Obstructive apnea/hypopnea event | Must fulfill criterion 1 or 2, plus criterion 3 of the following (13):<br>1. A clear decrease (>50%) from baseline in the amplitude of a valid measure of breathing during sleep. Baseline is defined as the mean amplitude of stable breathing and oxygenation in the two minutes preceding onset of the event (in individuals who have a stable breathing pattern during sleep) or the mean amplitude of the three largest breaths in the two minutes preceding onset of the event (in individuals without a stable breathing pattern).<br>2. A clear amplitude reduction of a validated measure of breathing during sleep that does not reach the above criterion but is associated with either an oxygen desaturation of >3% or an arousal.<br>3. The event lasts 10 seconds or longer | |
| | Obstructive Apnea Index in TST | events/hr. |
| | Total Apnea Index in TST | events/hr. |
| | Obstructive Hypopneas Index in TST | events/hr. |
| | Total Hypopneas Index in TST | events/hr. |
| | Obstructive Apnea-Hypopneas Index in TST | events/hr. |
| | Obstructive Apnea-Hypopneas Index in non-REM | events/hr. |
| | Obstructive Apnea-Hypopneas Index in REM | events/hr. |
| | Total Apnea-Hypopneas Index in TST | events/hr. |
| | Total Apnea-Hypopneas Index in non-REM | events/hr. |
| | Total Apnea-Hypopneas Index in REM | events/hr. |
| | Total Apnea-Hypopneas, Mean Duration | min |
| | Total Apnea-Hypopneas, Longest Event | min |

* - these variables were excluded from the main analyses as having more than 50% of missing values.

**Table E2. Description of health administrative datasets used**

| Dataset | Description | Available from |
|---|---|---|
| **RPDB** | Registered Persons' Database files. Basic demographic information (e.g., sex, year of birth, date of death where applicable and postal codes) about anyone who has ever received an Ontario health card number. | 1990 |
| **OHIP** | Ontario Health Insurance Plan Physician Services Claims Database. Information on all physician claims in the province. | 1991 |
| **CIHI-DAD /SDS** | Canadian Institute for Health Information Discharge Abstract Database (information on all acute care hospitalization in Canada) and the Same Day Surgery. | 1988 |
| **NACRS** | Canadian Institute for Health Information National Ambulatory Care Reporting System: Emergency (ED), Dialysis and Cancer Clinics. Information on all ED visits in the province. | ED: 2002 |
| **Census** | Contains aggregated data for Ontario and Canada that describe the general demographic information on 100% of the population and the remaining information for a 20% sample of the population. | 1991 |
| **IPDB** | ICES Physician database. It contains information about physician demographics, specialty training and certification and practice location. | 1992 |
| **ADP** | Assistive Devices Program. Information on all individuals who have had their CPAP equipment paid for by the province. | 2004 |
| **CHF** | Ontario Congestive Heart Failure Database. It contains all Ontario individuals identified as having CHF based on OHIP/NACRS, CIHI, and RPDB data. | 1991 |
| **COPD** | Ontario Chronic Obstructive Pulmonary Disease Database - Sensitive Definition. It contains all Ontario COPD patients based on OHIP, CIHI, and RPDB data. | 1988 |
| **HYPERTEN-SION** | Ontario Hypertension Database. It contains all Ontario hypertension patients based on OHIP, CIHI/SDS, and RPDB data. | 1988 |
| **ODD** | Ontario Diabetes Database. It contains all Ontario individuals identified as having diabetes based on OHIP, CIHI/SDS, and RPDB data. Once included, a person remains in the ODD until death or relocation outside of Ontario. | 1991* |
| **OMHRS** | Ontario Mental Health Reporting System stand-alone admissions dataset. OMHRS is a data holding at CIHI that includes information on all adult inpatient mental health beds in Ontario. It is based on the Resident Assessment Instrument-Mental Health and includes information about mental and physical health, social support and service use. | 2006 |
| **OCRD** | Ontario Cancer Registry Data. It contains information on all Ontario residents who have been newly diagnosed with cancer or who have died of cancer, except non-melanoma skin cancer. Data is collected from: CIHI/DAD; Pathology Reports (paper); Pathology Data (PIMS); Registered Person Database (MOHLTC); Registrar General (Mortality Data); Chemo/Radiation Clinic visits (Integrated Cancer Programs & Princess Margaret Hospital); Data from Other Provincial Registries. | 1985 |
| **ORGD** | Ontario Registrar General Death data. It contains information on all deaths occurring in Ontario. Probabilistic data linkage was used with the RPDB to assign IKNs to the ORGD records. | 1990 |

* - data is available from 1988 to 1991 for hospitalized diabetes only (from CIHI).

**Table E3. Description of variables derived from administrative data.**

| **Diseases** | **ICD-9-CM diagnostic codes** (prior to fiscal year 2002 and) | **ICD-10-CA code** (after fiscal year 2002) | **OHIP codes#** |
|---|---|---|---|
| **Primary outcome** | | | |
| ***Incident diabetes*** Diagnostic dates from the ODD after index date | The diagnosis date of diabetes mellitus (DM) was defined based on age at admission or service date as below:<br>(i). 1 or 2 OHIP dxcode 250 claims prior to 19th birth date and 1 OHIP claim after 19th birth date within 2 years, use 19th birth date as incident DM date.<br>(ii). 2 OHIP dxcode 250 claims or 1 OHIP feecode Q040, K029, K030 claim or 1 CIHI admission within 2 years for admission or service after 19th birth date, use the first date as incident DM date.<br>- all CIHI hospital discharges with a diagnosis of DM: ICD-9: 250 (any of dxcode), ICD-10: E10, E11, E13, E14 (any of dx10code);<br>- all OHIP physician billings with a diagnosis of DM: Diagnosis Code: 250, Feecodes: Q040, K029, K030. | | |
| **Secondary outcome** | | | |
| **All-causes mortality** from RPDB, Demographic | The date of the ***death from all-causes*** | | |
| **Main exposures or risk factors and other potential confounders** | | | |
| ***Prior AMI*** Any diagnosis of AMI in CIHI/DAD or OHIP associated with ED visits | 410.x, 412.x | I21, I22, I25.2 | 410, 412 |
| ***Prior stroke*** Any diagnosis of stroke in CIHI/DAD or OHIP associated with ED visits | 362.3, 430.x, 431.x, 433.x1, 434.x1, 436, 435.x | I60 (excl I60.8);<br>I61; I63 (excl I63.6); I64; H34.1<br>G45 (excl G45.4) | 432, 435, 436 |
| ***Prevalent hypertension*** | Diagnostic dates from HYPERTENSION database before index date | | |
| ***Prevalent CHF*** | Diagnostic dates from Ontario CHF database before index date | | |
| ***Prevalent diabetes*** | Diagnostic dates from the ODD before index date | | |
| ***Prevalent COPD*** | Diagnostic date from COPD dataset before index date | | |
| ***Prior depression*** the most responsible diagnosis of major depression in CIHI/DAD, and from OHIP dataset | 296.2, 296.3, 296.5, 300.4, 309.x, 311 | F20.4, F31.3-F31.5, F32.x, F33.x, F34.1, F41.2, F43.2 | 311, 300 |
| **Comorbidities at baseline** (any claims data from OHIP, CIHI, NACRS): low (0 to 5 ADGs) ; medium (6 to 10 ADGs) ; high (≥11 ADGs) | ***Comorbidities at baseline***: Using Hopkins ADGs, and using both OHIP and CIHI diagnosis codes with a three-year look back period from the index sleep study: ADG1-ADG34 (Aggregated Diagnostic Groups) | | |
| ***Prevalent cancer*** | Diagnostic dates from OCRD before index date | | |
| **Urban/rural status** | ***Urban/rural status*** at time of index diagnostic sleep study, from postal code | | |
| **Income status** based on the patient's postal code and Statistics Canada Postal Code Conversion File | Ontario neighbourhoods are classified into one of the five approximately equal-sized income quintiles, ranked from poorest (Q1) to wealthiest (Q5). Each patient was assigned to the income quintile at the time of diagnostic sleep study using the patient's postal code and Statistics Canada's Postal Code Conversion File | | |
| **CPAP claims** from ADP, from Apr 2004 to the last date of follow-up | Types of device prescribed were<br>CONTINUOUS PAP SYSTEM or "RESMED S8 COMPACT CPAP SYSTEM" or "RESMED S8 ELITE CPAP SYSTEM". | | |

*Inpatient hospitalizations are recorded in the Canadian Institute for Health Information Discharge Abstract (CIHI-DAD). Prior to April 2003, the CIHI-DAD also contained records of same day surgery encounters. As of April, 2003, same day surgery records are obtained from the National Ambulatory Care Reporting System (NACRS) database.
ED visits will be identified using physician billing claims obtained from the OHIP database.
# OHIP diagnostic codes except written OHIP feecodes.

**Sensitivity of results to unmeasured confounders**

***Methods***

Confounding bias is of particular concern in observational studies based on a secondary data analyses(14). Despite the wide spectrum of variables available from linked clinical and health administrative data, our study can be criticized for the incompleteness of information on potential confounders. For example, lack of information about frequency of blood glucose testing may bias estimates of the association between OSA and incident diabetes (Figure E2). **Figure E2** demonstrates our hypotheses on the confounding pathway that could bias the apparent association between OSA and incident diabetes. We hypothesized that (i) more blood glucose tests are associated with a higher likelihood of being screened and consequently diagnosed with diabetes (HR) (15); (ii) more severe OSA is associated with more health care resource utilization and consequently with a higher likelihood of being screened for diabetes (OR) (16).

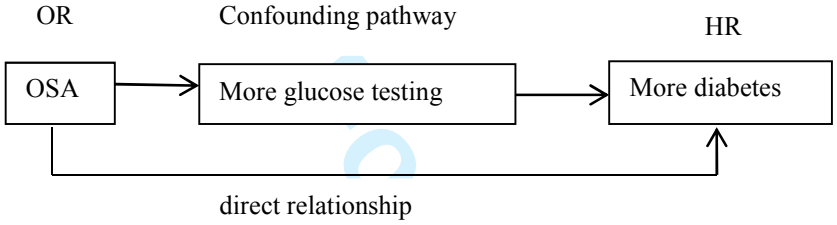


**Figure E3.** Effect of unmeasured confounding by glucose testing on the association between sleep apnea and incident diabetes

To assess the sensitivity of results to unmeasured confounders, we used the approach recommended by Lin et al, 1998 (17). This sensitivity analysis makes assumptions about potential residual confounding and quantifies its effect on the estimated hazard ratio for the association between OSA and outcomes of interest. The proposed approach assumes that "the true exposure effect can be represented in a regression model that includes the exposure indicator as well as the measured and unmeasured confounders". We used the corresponding reduced model - without unmeasured confounder - to make statistical inferences about the true exposure effect (e.g., severity of OSA) by first specifying: (i) the distribution of the unmeasured confounder (e.g., more blood glucose tests, Yes/No) in the exposed (e.g., AHI>30) and unexposed (e.g., AHI<5) groups; and (ii) the effect (hazard ratio) of the unmeasured confounder on the outcome (e.g., incident diabetes). To explore how strong unmeasured confounding must be to explain the significantly increased HRs observed in our studies, we examined the scenarios formed by combinations of the following assumptions: (i) the prevalence of the unmeasured confounder in the unexposed group ranged from 0 to 0.5; (ii) the prevalence of the unmeasured confounder in the exposed group ranged from 0 to 1; (iii) the strength of the association (HRs) between the unmeasured confounder and outcomes ranged from 1.5 to 5.

***Results***

Assessing the sensitivity of results to unmeasured confounders, we found that unmeasured confounders should increase both the hazard of incident diabetes and the probability of severe OSA (AHI>30 vs. AHI<5) from two and half to three-fold to change the association between incident diabetes and severe OSA from the observed value of 1.31 (95% CI: 1.07-1.61) to non-significant (Table E4).

**Table E4**. The point estimates and 95% confidence interval for the relative hazard of incident diabetes associated with severe sleep apnea with adjustment for an unmeasured binary confounder having relative hazard of incident diabetes of 3.

| | **P0** | | | | | |
|---|---|---|---|---|---|---|
| **P1** | **0** | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** |
| **0** | 1.31 (1.07, 1.61) | 1.57 (1.28, 1.93) | 1.83 (1.50, 2.25) | 2.10 (1.71, 2.58) | 2.36 (1.93, 2.90) | 2.62 (2.14, 3.22) |
| **0.1** | 1.09 (0.89, 1.34) | 1.31 (1.07, 1.61) | 1.53 (1.25, 1.88) | 1.75 (1.43, 2.15) | 1.97 (1.61, 2.42) | 2.18 (1.78, 2.68) |
| **0.2** | 0.94 (0.76, 1.15) | 1.12 (0.92, 1.38) | 1.31 (1.07, 1.61) | 1.50 (1.22, 1.84) | 1.68 (1.38, 2.07) | 1.87 (1.53, 2.30) |
| **0.3** | 0.82 (0.67, 1.01) | 0.98 (0.80, 1.21) | 1.15 (0.94, 1.41) | 1.31 (1.07, 1.61) | 1.47 (1.20, 1.81) | 1.64 (1.34, 2.01) |
| **0.4** | 0.73 (0.59, 0.89) | 0.87 (0.71, 1.07) | 1.02 (0.83, 1.25) | 1.16 (0.95, 1.43) | 1.31 (1.07, 1.61) | 1.46 (1.19, 1.79) |
| **0.5** | 0.66 (0.54,0.81) | 0.79 (0.64, 0.97) | 0.92 (0.75, 1.13) | 1.05 (0.86, 1.29) | 1.18 (0.96,1.45) | 1.31 (1.07, 1.61) |
| **0.6** | 0.60 (0.49, 0.73) | 0.72 (0.58, 0.88) | 0.83 (0.68, 1.03) | 0.95 (0.78, 1.17) | 1.07 (0.88, 1.32) | 1.19 (0.97, 1.46) |
| **0.7** | 0.55 (0.45, 0.67) | 0.66 (0.54, 0.81) | 0.76 (0.62, 0.94) | 0.87 (0.71, 1.07) | 0.98 (0.80, 1.21) | 1.09 (0.89, 1.34) |
| **0.8** | 0.50 (0.41, 0.62) | 0.61 (0.49, 0.74) | 0.71 (0.58, 0.87) | 0.81 (0.66, 0.99) | 0.91 (0.74, 1.12) | 1.01 (0.82, 1.24) |
| **0.9** | 0.47 (0.38, 0.58) | 0.56 (0.46, 0.69) | 0.66 (0.54, 0.81) | 0.75 (0.611,0.920) | 0.84 (0.69, 1.04) | 0.94 (0.76, 1.15) |
| **1** | 0.44 (0.36, 0.54) | 0.52 (0.43, 0.64) | 0.61 (0.50, 0.75) | 0.70 (0.57, 0.86) | 0.79 (0.64, 0.97) | 0.87 (0.71, 1.07) |

These analyses indicate that unmeasured confounding would need to be a relatively strong to be responsible for the association between incident diabetes and severity of OSA.

**Table E5.** Model fitting and effect of predictors expressed as HR and 95%CI controlling for sex, age, body mass index, history of smoking status, prior comorbidities (HTN, AMI, ADG categories) and income status (calculation was performed on dataset #3 (n= 8678, number of events= 1017)).

| OSA-related predictors | Model 1: AHI as continuous variable | | | | Model 2: AHI as categories | |
|---|---|---|---|---|---|---|
| | **Simplest** | **Simplest + Interaction of AHI with BMI#** | **Simplest + Interaction of AHI with age#** | **Simplest + transformed*: neck, BMI, age** | **Simplest** | **Simplest + transformed*: neck, BMI, age** |
| ***Symptoms and measurement*** | | | | | | |
| DS (Yes) | 1.17 (1.03-1.33) | 1.18 (1.04-1.34) | 1.17 (1.03-1.33) | 1.21 (1.06-1.37) | 1.18 (1.04-1.34) | 1.21 (1.07-1.38) |
| Neck circum., cm (42 vs. 36) | 1.17 (1.07-1.26) | 1.17 (1.07-1.27) | 1.16 (1.07-1.26) | 1.77 (1.41-2.24) | 1.16 (1.07-1.26) | 1.75 (1.39-2.21) |
| ***PSG indexes*** | | | | | | |
| AHI, total, events/hr (32 vs. 6) | 1.07 (1.00-1.14) | BMI=25: 1.22 (1.10-1.34)<br>BMI=40: 1.04 (0.98-1.11)<br>p=0.0013¥ | age=40: 1.11 (1.04-1.20)<br>age=70: 0.98 (0.88-1.09)<br>p=0.0326¥ | 1.06 (0.99-1.13) | — | — |
| 5≤AHI<15:AHI<5 | — | — | — | — | 1.30 (1.06-1.58) | 1.23 (1.0-1.50) |
| 15≤AHI≤30:AHI<5 | — | — | — | — | 1.33 (1.08-1.63) | 1.23 (1.0-1.51) |
| AHI>30:AHI<5 | — | — | — | — | 1.44 (1.18-1.77) | 1.31 (1.07-1.61) |
| TST, hours (6.4 vs. 4.9) | 1.05 (0.97-1.14) | 1.06 (0.98-1.14) | 1.06 (0.98-1.14) | 1.07 (1.00-1.16) | 1.07 (0.99-1.15) | 1.09 (1.01-1.17) |
| Heart rate, mean in TST, bpm (69 vs. 56) | 1.33 (1.23-1.44) | 1.32 (1.22-1.43) | 1.33 (1.23-1.43) | 1.31 (1.22-1.42) | 1.33 (1.24-1.44) | 1.32 (1.22-1.43) |
| **LR $\chi^2$**<br>**$R^2$**<br>**df** | 768.31<br>0.098<br>18 | 779.53<br>0.100<br>19 | 772.82<br>0.099<br>19 | 841.32<br>0.107<br>24 | 777.38<br>0.099<br>20 | 845.6<br>0.108<br>26 |
| **Optimism for $R^2$** | 0.0045 | — | — | 0.0053 | 0.0049 | 0.0054 |
| **Corrected C-index** | 0.746 | — | — | 0.749 | 0.745 | 0.749 |

**Simplest**: predictors were controlled for sex, age, body mass index, history of smoking status, prior comorbidities (HTN, AMI, ADG categories) and income status without transformation for continuous variables.

*Significant non-linearity was observed for BMI, age, neck circumference – restricted cubic spline transformation with 4 knots was used.

# In statistical models with some variables transformed, similar trends for BMI and age were observed; however, the interactions with transformed variables contained many parameters were not always statistically significant.

Ɏ: For example, for a person with BMI of 25, the HR was 1.22 (95%CI: 1.10-3.34) comparing an AHI of 32 events/hour to 6 events/hour, while for a person with a BMI of 40, the HR was 1.04 (95%CI: 0.98-1.11). Decreasing HRs for AHI was also observed with increasing age. For a person with age of 40 years old the HR was 1.11 (95%CI: 1.04-1.20) comparing an AHI of 32 events/hour to 6 events/hour, while for a person with age of 70 the HR was 0.98 (95%CI: 0.88-1.09). In statistical models with some variables transformed, similar trends for BMI and age were observed; however, the interactions with transformed variables contained many parameters were not always statistically significant.

ADG – aggregated diagnosis groups; AHI – apnea-hypopnea index; AMI – acute myocardial infarction; BMI – body mass index; CI – confidence interval; df – degree of freedom; DS – daytime sleepiness; HTN – hypertension; HR – hazard ratio; HTN – hypertension; LR – likelihood ratio; PSG - polysomnography; TST - total sleep time.

**Table E6.** Model fitting and effect (HR and 95%CI) of severity of obstructive sleep apnea expressed by AHI on diabetes development, controlling for potential confounders and risk factors for diabetes.

| | Sample with excluded split-study (n total= 8678, number of events=1017) | | Sample with included split-study (n total= 8843, number of events=1035) | |
|---|---|---|---|---|
| **OSA-related predictors** | **Model 1** | **Fully adjusted model** | **Model 1** | **Fully adjusted model** |
| **AHI total as a continuous variable** | | | | |
| AHI, total, events/hr (32 vs. 6) | 1.13 (1.06-1.20) | 1.06 (0.99-1.13) | 1.12 (1.06-1.20) | 1.06 (0.99-1.13) |
| $R^2$ | 0.10 | 0.11 | 0.09 | 0.10 |
| **AHI as a categorical variable (reference group: AHI<5 events/hr)** | | | | |
| 5≤AHI<15 | 1.18 (0.97-1.44) | 1.23 (1.00-1.50) | 1.19 (0.98-1.49) | 1.23 (1.01-1.51) |
| 15≤AHI≤30 | 1.24 (1.01-1.53) | 1.23 (1.00-1.51) | 1.27 (1.04-1.57) | 1.26 (1.03-1.51) |
| AHI>30 | 1.47 (1.20-1.79) | 1.31 (1.07-1.61) | 1.45 (1.19-1.78) | 1.31 (1.07-1.60) |
| $R^2$ | 0.10 | 0.11 | 0.09 | 0.10 |
| Control variables | sex, age*, BMI*, history of smoking status, prior comorbidities within 3-year look-back window (HTN, MI, ADG categories) and income status | Model 1 + daytime sleepiness, neck circumference*, heart rate in sleep, and TST | sex, age*, BMI*, history of smoking status, prior comorbidities within 3-year look-back window (HTN, MI, ADG categories) and income status | Model 1 + daytime sleepiness, neck circumference*, heart rate in sleep, and TST |

*Significantly non-linear – restricted cubic spline transformations with 4 knots were used.

ADG – aggregated diagnosis groups; AHI – apnea-hypopnea index; AMI – acute myocardial infarction; BMI – body mass index; CI – confidence interval; df – degree of freedom; DS – daytime sleepiness; HTN – hypertension; HR – hazard ratio; HTN – hypertension; LR – likelihood ratio; TST - total sleep time.

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