Association of Sleep Apnea and Type II Diabetes
A Population-based Study

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Rationale: Cross-sectional association has been reported between sleep-disordered breathing (SDB) and insulin resistance, but no prospective studies have been performed to determine whether SDB is causal in the development of diabetes.
Objectives: The purpose of our study was to investigate the prevalence and incidence of type II diabetes in subjects with SDB and whether an independent relationship exists between them.
Methods: A cross-sectional and longitudinal analysis was performed in 1,387 participants of the Wisconsin Sleep Cohort. Full polysomnography was used to characterize SDB. Diabetes was defined in two ways: (*1*) physician-diagnosis alone or (*2*) for those with glucose measurements, either fasting glucose $\geqslant$ 126 mg/dl or physician diagnosis.
Measurements and Main Results: There was a greater prevalence of diabetes in subjects with increasing levels of SDB. A total of 14.7% of subjects with an apnea–hypopnea index (AHI) of 15 or more had a diagnosis of diabetes compared with 2.8% of subjects with an AHI of less than 5. The odds ratio for having a physician diagnoses of diabetes mellitus with an AHI of 15 or greater versus an AHI of less than 5 was 2.30 (95% confidence interval, 1.28–4.11; p = 0.005) after adjustment for age, sex, and body habitus. The odds ratio for developing diabetes mellitus within 4 yr with an AHI of 15 or more compared with an AHI of less than 5 was 1.62 (95% confidence interval, 0.67–3.65; p = 0.24) when adjusting for age, sex, and body habitus.
Conclusions: Diabetes is more prevalent in SDB and this relationship is independent of other risk factors. However, it is not clear that SDB is causal in the development of diabetes.

Keywords: diabetes; incidence; prevalence; sleep apnea

Sleep-disordered breathing (SDB) and diabetes mellitus (DM) are prevalent diseases that share several risk factors, including advanced age and obesity (1, 2). Diabetes was the sixth leading cause of death listed on U.S. death certificates in 2003 and is associated with a higher incidence of cardiovascular, cerebrovascular, and renal disease (3, 4). There is also mounting evidence that SDB may be an independent risk factor for cardiovascular and cerebrovascular disease (5). Interest in a potential independent link between the two diseases continues to grow.

Several studies have explored this relationship with conflicting results. Four recent studies demonstrated an inverse relationship between apnea–hypopnea index (AHI) and insulin sensitivity (6–9). The relationship was independent of body mass index (BMI) and age in all three studies. Another study found a relationship between fasting insulin levels and increasing AHI in patients with BMI of 29 or greater, but not in those with lower BMIs (10). Finally, Stoohs and colleagues found the relationship between worsening insulin sensitivity and SDB in a group of 50 "healthy, normotensive individuals" was completely accounted for by increased BMI (11). The primary objective of these studies was to explore the relationship between insulin sensitivity, or surrogates thereof, and SDB at a single time point. The preponderance of evidence supports the theory that SDB independently contributes to a decrease in insulin sensitivity.

However, the relationship between SDB and diabetes is less understood and less well studied. A few studies have attempted to evaluate the cross-sectional relationship with mixed results (12–15).

Whether SDB contributes to the development of DM is also unknown. Two recent population studies using questionnaire-based research found that reported "habitual" or "regular" snoring was an independent risk for the development of diabetes (16, 17). These studies did not involve any objective measures of sleep apnea, leaving uncertainty about the relationship between SDB and diabetes mellitus. Although insulin resistance is a known risk factor for the development of diabetes and, as discussed previously, there is evidence that SDB contributes to insulin resistance, the current body of evidence does not answer the question about whether SDB is an independent risk factor for developing diabetes. A more definitive understanding of the interaction between these diseases would provide important guidance to health care providers who manage them.

The purpose of our study was to investigate the prevalence and incidence of type II diabetes in patients with SDB and whether an independent relationship exists between them. This study is novel in its longitudinal design and use of full nocturnal polysomnography (PSG) to evaluate SDB. Some of the results of these studies have been previously reported in the form of an abstract (18).

METHODS

Participants

Baseline and follow-up data from 1,387 participants in the Wisconsin Sleep Cohort, a population-based longitudinal study of sleep disorders, were used for this investigation. The protocols and informed-consent documents were approved by the Institutional Review Board of the University of Wisconsin Medical School. The design of the cohort is discussed elsewhere (2) and in the online supplement.

Data Collection

The overnight protocol included full PSG (polygraph model 78; Grass Instruments, Quincy, MA) and standard anthropometric methods to obtain weight, height, waist girth, and other measures of body habitus. Details of the PSG measurements and definitions can be found in the online supplement.

A questionnaire was completed at each visit and included questions about personal health history, sleep habits and problems, and lifestyle.

Participants who reported being diagnosed with diabetes by a physician provided the date of diagnosis and treatment.

The morning after the sleep study, a venipuncture was performed for fasting plasma glucose. The blood draw did not become part of the protocol until 1993 (the first follow-up visit for most subjects). Diabetes was defined in two ways: (*1*) report of physician-diagnosed diabetes alone or (*2*) for those with glucose measurements, either fasting glucose of 126 mg/dl or greater or physician-diagnosed diabetes. They were further categorized as "type I" if they were diagnosed before 30 yr of age or had BMI of less than 25 and were treated with insulin alone. They were categorized as "type II" if their treatment regimen included oral hypoglycemic agents or they were managed with lifestyle modifications. We were interested in the relationship between SDB and type II DM; therefore, we excluded people with type I diabetes from the analysis.

Statistical Analysis

All analyses were performed using SAS/STAT 9.1 (SAS Institute, Cary, NC). Odds ratios (ORs) for prevalent type II diabetes (both definitions) with two levels of SDB (AHI 5–15 and AHI $\geq$ 15, both vs. AHI < 5) were estimated using multiple logistic regression. To examine more severe SDB, we also examined ORs for diabetes with AHI of 30 or greater versus AHI of less than 5. A linear contrast was used to test for trend. Generalized estimating equations with an exchangeable working correlation were used to account for within-subject correlation and to produce robust standard errors for hypothesis tests and confidence intervals (CIs). ORs were examined with adjustment for sex and age only and with adjustment for body habitus measures. We found that waist girth was the body habitus measure with the best correlation with diabetes, which was consistent with a recent report (19). When including both BMI and waist girth in models of diabetes, BMI was no longer significant; therefore, we chose to use waist girth (with an interaction with sex when significant) as our body habitus measure. Other potentially confounding variables were examined to determine if they significantly changed the SDB–diabetes relationship.

To examine 4-yr incidence of diabetes, subjects with diabetes at their first visit or with only a single visit were excluded from the data. ORs of developing diabetes at the end of a 4-yr period for two levels of SDB (measured at the beginning of the period) were estimated using multiple logistic regression. Generalized estimating equations were used to account for within-subject correlation for subjects with more than one at-risk 4-yr period for developing diabetes. A similar procedure was used for 8-yr incidence. We used subject "visits" rather than individuals to improve the power of our study to detect independent relationships.

RESULTS

A total of 1,387 subjects (2,524 visits) were included in the cross-sectional analysis. Forty-one subjects were excluded from the original sample of 1,428 subjects because of missing or insufficient data or type 1 diabetes. Characteristics of the sample are shown in Table 1. The mean age of the group was 49.0 yr ($\pm$ 8.3) with a median BMI of 28.9 kg/m^2 (interquartile range, 25.5–33.3);

23% of subjects had an initial AHI of 5 or greater (26% of all visits).

The cumulative prevalence of type II diabetes in the cross-sectional sample was 4.2% (Table 2). There was a greater prevalence of diabetes in subjects with increasing levels of SDB. A total of 14.7% of subjects with an AHI of 15 or greater had a diagnosis of diabetes compared with 2.8% of subjects with an AHI of less than 5. When weighted for the original sampling scheme, the cumulative prevalence of DM was 3.6%.

The OR for having physician-diagnosed DM with an AHI of 5–15 compared with an AHI of less than 5 was 1.83 (95% CI, 1.07–3.11; p = 0.026; Table 3) when adjusted for age and sex. When comparing those with an AHI of 15 versus an AHI of less than 5, the OR was 4.75 (95% CI, 2.62–8.63; p < 0.0001). When body habitus measures (waist girth and waist girth $\times$ sex interaction) were included in the model, the OR for mild SDB (AHI 5–15) was no longer significant (OR, 1.25; 95% CI, 0.75–2.07; p = 0.40). Although there was attenuation of the OR for more severe SDB (AHI $\geq$ 15), it remained statistically significant with an OR of 2.30 (95% CI, 1.28–4.11; p = 0.0052). When comparing those with an AHI of 30 or greater with those with an AHI of less than 5, the OR was 3.48 (95% CI, 1.69–7.18; p = 0.0007); there was also a significantly increasing trend (p = 0.0009).

To provide a more inclusive definition of diabetes, we also did cross-sectional analysis defining diabetes as either fasting glucose of 126 mg/dl or greater or of physician-diagnosed diabetes. Because we did not start collecting blood glucose until 4 yr after the initiation of the cohort, we had fewer subjects and observations (1,552 visits from 1,117 subjects). When adjusted for age, sex, and body habitus, the OR for having DM with an AHI of 5–15 compared with an AHI of less than 5 was 1.14 (95% CI, 0.76–1.71; p = 0.54). The OR for DM with an AHI of 15 or greater versus an AHI of less than 5 was 1.67 (95% CI, 1.04–2.67; p = 0.03). The results were similar when comparing an AHI of 30 or greater versus an AHI of less than 5 (OR, 1.79; 95% CI, 1.02–3.12; p = 0.04; test for trend: p = 0.026).

Our longitudinal analysis included 978 subjects (representing 1,857 4-yr follow-up periods) from the larger cohort who reported no diagnosis of diabetes on the first visit of each 4-yr period and had at least one follow-up visit. The OR for having a diagnosis of DM on a follow-up visit for those with an initial AHI of 5–15 compared with those with an AHI of less than 5 when adjusting for age and sex was 2.81 (95% CI, 1.51–5.23; p = 0.001; Table 4). The OR decreased to 1.56 when adjusted for age, sex, and body habitus, and this was no longer significant (95% CI, 0.80–3.02; p = 0.19). Similarly, the OR for developing DM with an AHI of 15 or greater compared with an AHI of less than 5 was 4.06

TABLE 1. CHARACTERISTICS OF THE CROSS-SECTIONAL SAMPLE—2,517 VISITS FROM 1,382 PARTICIPANTS (779 MEN, 603 WOMEN)

	AHI < 5	AHI 5–15	AHI $\geq$ 15	All
Observations, n (% all)	1,861 (73.7)	414 (16.4)	249 (9.9)	2,524
Age, yr, mean (SD)	48.0 (8.0)	51.7 (8.2)	52.1 (8.3)	49.0 (8.3)
BMI, median (Q1, Q3)	27.9 (24.7–31.7)	32.0 (27.8–36.6)	34.2 (30.7–39.9)	28.9 (25.5–33.4)
Waist girth, cm				
Women: mean (SD)	89.1 (15.7)	102.0 (14.9)	114.5 (16.4)	92.1 (17.1)
Men: mean (SD)	97.1 (11.3)	105.2 (12.6)	111.7 (15.1)	100.6 (13.2)
Total sleep time, h, mean (SD)	6.2 (1.0)	6.3 (1.0)	6.0 (1.1)	6.2 (1.0)
Usual sleep, h, mean (SD)	7.1 (0.9)	7.2 (0.9)	7.1 (1.1)	7.1 (0.9)
Exercise per wk, h, mean (SD)	2.5 (2.9)	2.0 (2.7)	2.1 (3.1)	2.4 (2.9)
Current cigarette smoker, n (%)	323 (17.4)	70 (16.9)	37 (14.9)	430 (17.1)

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; Q1, Q3 = interquartile range.

TABLE 2. DIAGNOSED TYPE II DIABETES BY INITIAL APNEA–HYPOPNEA INDEX STATUS

| Initial AHI | n | Type II Diabetes Diagnosis, n (%) | | |
		Initial	Follow-up	Cumulative
< 5	1,072	17 (1.6)	13 (1.2)	30 (2.8)
5–15	199	6 (3.0)	5 (2.5)	11 (5.5)
≥ 15	116	9 (7.8)	8 (6.9)	17 (14.7)
All	1,387	32 (2.3)	26 (1.9)	58 (4.2)

Definition of abbreviation: AHI = apnea–hypopnea index.

(95% CI, 1.86–8.85; p = 0.0004), with adjustment for age and sex, but decreased to 1.62 when body habitus measures were included in the model. The CI included unity and thus the OR was no longer statistically significant (95% CI, 0.67–3.65; p = 0.24). When using a more severe degree of SDB (AHI ≥ 30 vs. AHI < 5), the results were essentially unchanged and there was no significant trend. Using the alternative definition of diabetes (physician-diagnosed diabetes or fasting glucose ≥ 126 mg/dl), neither level of SDB was a significant risk for developing DM when adjusted for age and sex only or with additional adjustment for body habitus (Table 5); the test for trend was also not statistically significant. We also looked at 8-yr incidence data and found similar results (data not shown).

In an attempt to control for sleep deprivation as a mechanism for a relationship between SDB and DM, we included the objective measure of "total sleep time" from PSG analysis as well as the subjective report of "usual sleep time" from questionnaire data in the longitudinal and cross-sectional analyses. Recently, it was demonstrated that reported sleep time of fewer than 6 h was independently associated with prevalent diabetes; however, similar to the report of Punjabi and colleagues, including objective and subjective measures of sleep time in the model did not explain the relationship (8, 20). We also examined sleepiness using an Epworth Sleepiness Scale score of 11 or greater to determine if more symptomatic participants had a higher risk of developing diabetes. There was no significant change in the OR for the two AHI levels in either the cross-sectional or longitudinal models when sleepiness was included in the models.

The majority of subjects with SDB in the cohort have not been diagnosed with obstructive sleep apnea syndrome and do not use continuous positive airway pressure. If, as hypothesized, SDB does lead to a greater likelihood of developing DM, continuous positive airway pressure use might reduce the effect of SDB. However, excluding the 37 subjects who began using continuous positive airway pressure resulted in no significant change in our

TABLE 4. ODDS RATIOS FOR 4-YR INCIDENCE OF PHYSICIAN-DIAGNOSED DIABETES FOR TWO LEVELS OF SLEEP-DISORDERED BREATHING

	Odds Ratio	95% Confidence Interval	p Value
Adjusted for sex and age			
AHI 5–15 vs. AHI < 5	2.81	1.51–5.23	0.001
AHI ≥ 15 vs. AHI < 5	4.06	1.86–8.85	0.0004
Adjusted for sex, age, and body habitus*			
AHI 5–15 vs. AHI < 5	1.56	0.80–3.02	0.19
AHI ≥ 15 vs. AHI < 5	1.62	0.67–3.65	0.24

Definition of abbreviation: AHI = apnea–hypopnea index.
* Body habitus measures: waist girth.

findings. Similarly, controlling for smoking did not alter any of these results.

DISCUSSION

The Wisconsin Sleep Cohort provided a unique opportunity to investigate the relationship between diabetes and SDB with both a cross-sectional and prospective designs. In the cross-sectional study, we found that self-reported diabetes was three to four times more prevalent in subjects with an AHI of 15 or greater than in those with an AHI of less than 5. An independent relationship remained even after controlling for shared risk factors such as age, sex, and body habitus. A significant independent association was also found when we used a more inclusive definition of diabetes that included either physician diagnosis or elevated fasting blood glucose. However, we did not find a statistically significant independent causal effect in the development of type II diabetes in our prospective analysis. The incidence of diabetes over a 4-yr follow-up period was not significantly related to the severity of SDB at the time of initial enrollment in the cohort when shared risk factors were taken into account.

Similar to Punjabi and colleagues (8), we were not able to demonstrate that including measures of sleep time in the model explained the relationship. Although all hypopnea events were marked by oxyhemoglobin desaturation of 4% or greater, we did not have data expressed as the percentage of sleep time at or below oxygen saturation cut points. Others have demonstrated an association between overall desaturation exposure and impaired glucose utilization (6, 7). However, many cardiovascular and respiratory diseases and conditions can contribute to lower oxygenation during sleep, so these associations do not necessarily reflect effects of SDB.

TABLE 3. ODDS RATIOS FOR PREVALENT, PHYSICIAN-DIAGNOSED DIABETES FOR TWO LEVELS OF SLEEP-DISORDERED BREATHING

	Odds Ratio	95% Confidence Interval	p Value
Adjusted for sex and age			
AHI 5–15 vs. AHI < 5	1.83	1.07–3.11	0.026
AHI ≥ 15 vs. AHI < 5	4.75	2.62–8.63	< 0.0001
Adjusted for sex, age, and body habitus*			
AHI 5–15 vs. AHI < 5	1.25	0.75–2.07	0.40
AHI ≥ 15 vs. AHI < 5	2.30	1.28–4.11	0.005

Definition of abbreviation: AHI = apnea–hypopnea index.
* Body habitus measures: waist girth and waist girth × sex interaction.

TABLE 5. ODDS RATIOS FOR 4-YR INCIDENCE OF FASTING GLUCOSE ≥ 126 mg/dl OR PHYSICIAN-DIAGNOSED DIABETES FOR TWO LEVELS OF SLEEP-DISORDERED BREATHING

	Odds Ratio	95% Confidence Interval	p Value
Adjusted for sex and age			
AHI 5–15 vs. AHI < 5	1.75	(0.93–3.29)	0.08
AHI ≥ 15 vs. AHI < 5	1.88	(0.73–4.83)	0.19
Adjusted for sex, age, and body habitus*			
AHI 5–15 vs. AHI < 5	1.00	(0.49–2.02)	0.85
AHI ≥ 15 vs. AHI < 5	0.91	(0.36–2.33)	0.85

Definition of abbreviation: AHI = apnea–hypopnea index.
* Body habitus measures: waist girth.

To our knowledge, our study is the first to look longitudinally at a large cohort of subjects with full PSG-evaluated SDB to determine if higher levels of SDB resulted in a greater likelihood of developing diabetes. Previous prospective studies have used snoring as a surrogate for SDB without the benefit of nocturnal PSG (16, 17). The conclusion from these previous studies is that snoring is an independent risk factor for the development of diabetes. It is unlikely that the subjects categorized as having "habitual" and "regular" snoring had worse SDB (i.e., AHI > 50) compared with the group we studied; the specificity of snoring for severe SDB is not high (21, 22). Although we cannot be sure of the reason for the disparity with the previous studies, use of PSG allowed a more precise quantification of the magnitude of SDB and its relationship to the development of diabetes over time.

We must reconcile our findings of an association of SDB with diabetes in the cross-sectional study, and the lack of an independent causal effect in the prospective, longitudinal analysis. Several cross-sectional studies have indicated that increasing levels of AHI are independently associated with worsened insulin resistance and glucose intolerance (6–9). There have been no prospective studies done that demonstrate a causal relationship between SDB and insulin resistance. Diabetes is often preceded by a "prediabetic" state including insulin resistance, impaired glucose tolerance, and possibly impaired fasting glucose, but the progression from one of these conditions to diabetes is variable and not well defined (23–26). It is possible that SDB does independently impair the body's use of glucose without altering the progression to DM. One widely accepted theory on the development of type II DM is that insulin resistance precedes DM and, in certain individuals, some of whom may have a genetic predisposition, the insulin secretion falters and diabetes ensues (27). SDB may not affect this last step, independent of other factors such as increased obesity, age, or genetic predisposition.

One potential conclusion from our data is that SDB contributes to weight gain and obesity and this leads to an increased risk of developing diabetes. It may be that persons with SDB gain more weight, especially centrally, than those without sleep apnea, which would lead to an increased incidence of diabetes. Whether those with SDB become more obese than matched control subjects is uncertain (28–31). Sleep curtailment has been shown to increase appetite (32). In addition, it has been shown that people with untreated obstructive sleep apnea had higher leptin levels, suggesting that obstructive sleep apnea is associated with resistance to the weight reduction effects of leptin (29). There is some biologic plausibility to the possibility that sleep apnea results in increased weight gain (29). Other possibilities for our findings include some predisposing risk factor, such as a genetic predisposition, that leads to an increased likelihood of developing diabetes and SDB in parallel. In addition, half of the participants with diabetes had preexisting diabetes when they enrolled in the cohort and were excluded from the longitudinal analysis of incident diabetes. It is possible that the most "susceptible" subjects had already developed diabetes, leaving those more "resistant" to the adverse metabolic effects of sleep apnea in the prospective analysis. Prospective studies of younger cohorts may be needed to determined if the effects of SDB occur earlier in the natural history of diabetes. It has been tempting to speculate that because the preponderance of evidence supports worsened insulin sensitivity and glucose utilization in those with SDB that this would lead to more diabetes. However, our data do not clearly support this and it underscores the complexity of the pathway from insulin resistance to the diabetic state and the difficulty in predicting who will go on to develop diabetes (33). It is important to remember that the studies looking at SDB and insulin resistance have been cross-sectional in design. There are no published prospective studies demonstrating an increased propensity for persons with SDB to develop insulin resistance or glucose intolerance.

Finally, diabetes may be causal in the development of SDB, as some have hypothesized. An analysis of the Sleep Heart Health Study found that people with diabetes had more episodes of periodic breathing than did those without diabetes (15). In addition, several smaller studies have looked at whether people with diabetes are more likely to have disordered breathing during sleep. It has been proposed that the autonomic dysfunction that may occur in those with DM could lead to this breathing instability (34–38). There are not enough subjects in our cohort with diabetes at baseline to have adequate power to examine whether they are more likely to develop SDB or have worsening of their AHI. It is possible that diabetes, either by autonomic instability or some other undefined mechanism including an inflammatory process, may lead to more breathing abnormalities during sleep. Alternatively, the leptin resistance noted in obstructive sleep apnea could be a potential mechanism for nocturnal respiratory instability because leptin deficiency has been associated with depressed respiratory control (39). If diabetes predisposes to the development of SDB, this could explain why we see a statistically significant cross-sectional relationship, but no clear evidence that SDB independently predisposes to developing diabetes.

Our study has several limitations. First, our classification of diabetes does not meet the American Diabetes Association's clinical criteria but is an accepted method for epidemiologic studies (40). We used report of physician-diagnosed diabetes, supported by details of the date of diagnosis and treatment, or fasting glucose rather than glucose tolerance testing, which may have resulted in misclassification. We had fewer subjects with fasting glucose data, but when using either physician-diagnosed diabetes or fasting glucose to define a diagnosis of "diabetes," we found similar results. A second limitation is that we had a relatively small number of participants in the cohort who developed diabetes during follow-up. Diabetes is a multifactorial disease, and if sleep apnea only contributes a small additional risk, we may not have had enough subjects to demonstrate a statistically significant risk. Furthermore, we may not have had a severe enough exposure group to demonstrate a statistically significant risk that may exist with more severe SDB. Approximately 4% of studies were in the category of an AHI of 30 or greater. A third concern is the possibility of a latent period that could extend beyond the duration of our study. We found no difference in the 8-yr incidence data compared with the 4-yr data, but even 8 yr may not have been long enough to demonstrate an exposure effect. A final limitation is that we were not easily able to separate our subjects with SDB into those with purely obstructive disease versus more central or mixed patterns of disease, which may have allowed us to see if a particular type of SDB was more associated with diabetes as some have proposed (15). However, the prevalence of central sleep apnea in other population studies is extremely low (15, 41). Because the average age of our sample was lower, we expect an even lower prevalence of central sleep apnea. Furthermore, this type of classification would be more important if we were looking at diabetes as a cause of SDB. Because our study population was 96% white, it is uncertain whether our findings can be generalized to other racial groups; the role of SDB in the development of diabetes may differ in other ethnic groups. There are ethnic groups with a greater prevalence of diabetes even at lower BMIs. Sleep apnea may have a different effect in these populations (42, 43).

Diabetes and SDB are two common conditions that are associated with significant morbidity. Although our data do not provide evidence for a causal link between these two conditions, the findings from our population-based investigation have clinical

relevance. The strong association of SDB with diabetes supports the need for a lower threshold for sleep evaluation referral in patients with diabetes and vigilance in those taking care of patients with SDB to consider the possibility of concurrent diabetes. Furthermore, treatment of sleep apnea improves insulin sensitivity and could benefit the metabolic profiles of these patients, although this is not well defined (44–47). Thus, treatment of SDB in patients with diabetes may still be beneficial, whether SDB has an indirect or direct role.

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