Diabetes and Sleep Disturbances

Findings from the Sleep Heart Health Study

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OBJECTIVE — To test the hypothesis that diabetes is independently associated with sleep-disordered breathing (SDB), and in particular that diabetes is associated with sleep abnormalities of a central, rather than obstructive, nature.

RESEARCH DESIGN AND METHODS — Using baseline data from the Sleep Heart Health Study (SHHS), we related diabetes to *1*) the respiratory disturbance index (RDI; number of apneas plus hypopneas per h of sleep); *2*) obstructive apnea index (OAI; ≥3 apneas/h of sleep associated with obstruction of the upper airway); *3*) percent of sleep time <90% O_2 saturation; *4*) central apnea index (CAI; ≥3 apneas [without respiratory effort]/h sleep); *5*) occurrence of a periodic breathing (Cheyne Stokes) pattern; and *6*) sleep stages. Initial analyses excluding persons with prevalent cardiovascular disease (CVD) were repeated including these participants.

RESULTS — Of the 5,874 participants included in this report, 692 (11.8%) reported diabetes or were taking oral hypoglycemic medications or insulin and 1,002 had prevalent CVD. Among the 4,872 persons without CVD, 470 (9.6%) had diabetes. Diabetic participants had worse CVD risk factor profiles than their nondiabetic counterparts, including higher BMI, waist and neck circumferences, triglycerides, higher prevalence of hypertension, and lower HDL cholesterol ($P < 0.001$, all). Descriptive analyses indicated differences between diabetic and nondiabetic participants in RDI, sleep stages, sleep time <90% O_2 saturation, CAI, and periodic breathing ($P < 0.05$, all). However, multivariable regression analyses that adjusted for age, sex, BMI, race, and neck circumference eliminated these differences for all sleep measures except percent time in rapid eye movement (REM) sleep (19.0% among diabetic vs. 20.1% among nondiabetic subjects, $P < 0.001$) and prevalence of periodic breathing (odds ratio [OR] for diabetic subjects versus nondiabetic subjects 1.80, 95% CI 1.02–3.15). Additionally, adjusted analyses showed diabetes was associated with nonstatistically significant elevations in the odds of an increased central breathing index (OR 1.42, 95% CI 0.80–2.55). Addition to the analysis of the 1,002 persons with prevalent CVD (including 222 people with diabetes) did not materially change these results.

CONCLUSIONS — These data suggest that diabetes is associated with periodic breathing, a respiratory abnormality associated with abnormalities in the central control of ventilation. Some sleep disturbances may result from diabetes through the deleterious effects of diabetes on central control of respiration. The high prevalence of SDB in diabetes, although largely explained by obesity and other confounders, suggests the presence of a potentially treatable risk factor for CVD in the diabetic population.

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Abbreviations: CAI, central apnea index; CVD, cardiovascular disease; EEG, electroencephalogram; OAI, obstructive apnea index; PSG, polysomnography; RDI, respiratory disturbance index; SDB, sleep-disordered breathing; SHHS, Sleep Heart Health Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Some risk factors for diabetes, including obesity, visceral adiposity, and advancing age, are also associated with sleep-disordered breathing (SDB). Evidence from a growing body of research suggests that SDB is associated with adverse cardiovascular disease (CVD) risk factors and outcomes, including hypertension and myocardial infarction (1–3). Similarly, CVD risk is substantially elevated among people with diabetes (4,5). Since diabetes and SDB not only share important risk factors, but also may be associated with CVD, the two conditions may be related to one another.

Diabetes may be a cause or consequence of SDB, or possibly both. One study showed that experimentally induced acute sleep deprivation can cause a state of glucose intolerance (6). Other studies demonstrated cross-sectional relationships between sleep apnea and both fasting insulin and insulin resistance (1,7–10) and between sleep apnea and overt diabetes (11). Snoring, which is a common symptom of SDB, has also been shown to predict the onset of diabetes in both men and women (12,13).

Other reports suggest that diabetic complications, particularly diabetic autonomic neuropathy, may be associated with ventilatory dysfunction. One study showed that 25% of diabetic individuals with autonomic neuropathy have sleep apnea, a proportion greater than in diabetic subjects without autonomic neuropathy (14). Diminished heart rate variability, a common manifestation of autonomic neuropathy, (15) is present in people with SDB (16) and may contribute to the increased CVD observed in both diabetes and SDB. In addition to its known association with diminished cardiovascular reflexes, diabetic autonomic neuropathy may be associated with impaired central control of respiration (17–21).

This report takes a general approach to these postulated relationships by testing the hypothesis that diabetic individuals experience more SDB than nondiabetic individuals, after adjustment for risk factors that are common to both dia-

betes and SDB. Of particular interest was the hypothesis that breathing abnormalities of a central, rather than obstructive, nature would be more common in individuals with diabetes.

RESEARCH DESIGN AND METHODS

The Sleep Heart Health Study: design and parent cohorts

The Sleep Heart Health Study (SHHS) is a multicenter longitudinal study designed to determine the cardiovascular and other consequences of SDB. The design and objectives of SHHS, as well as detailed descriptions of its member cohorts, protocols, and quality control procedures, have been published (22,23). Briefly, the SHHS consists of an ethnically diverse cohort of men and women aged ≥40 years who were members of existing parent cohorts. Parent cohorts include the Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Framingham Heart Study, Strong Heart Study, New York Hypertension Cohorts, Tucson Epidemiologic Study of Airways Obstructive Diseases, and the Health and Environment Study. The SHHS baseline examination was conducted between December 1995 and January 1998. Following a rigorous review (23), data from 6,441 participants constitute the SHHS cohort. Detailed SHHS documentation, including protocols, data collection forms, and manuals of operation are available (24).

Collection of sleep data

All participants underwent in-home electroencephalogram (EEG)-based overnight polysomnography (PSG) using Compumedics PS (Melbourne, Australia) equipment. Data were collected on 12 channels and included oximetry (Nonin, Minnesota), heart rate, chest wall and abdominal movement (by respiratory inductance plethysmography), nasal/oral airflow (Thermocouple; Protec), body position, EEG, electrooculogram (EOG), chin electromyogram (EMG), and electrocardiogram (ECG). A key feature of the SHHS is the variety of measures collected during the SHHS PSG. These data permit distinction among various features of SDB that may have distinct etiology and risk factors.

Technicians traveled to participants' homes in the evening to connect the PSG, collect anthropometric data, administer questionnaires, and provide instructions to participants about handling the equipment. Technicians returned to participants' homes in the morning to collect the equipment. Upon returning to the field centers, technicians downloaded the sleep data and sent it to the PSG Reading Center for processing (23,24).

Measures of sleep disturbance

Data on several distinct aspects of SDB are included in this report. These features are categorized as either respiratory parameters or features of sleep architecture.

Respiratory parameters

***1*) Respiratory disturbance index.** The respiratory disturbance index (RDI) is the number of apneas plus hypopneas per hour of sleep. An apnea is a complete or near complete cessation of airflow. Apneas were identified if the amplitude of the airflow or respiratory band data decreased to <25% of baseline amplitude (a period of regular breathing with stable oxygen levels) if the change lasted ≥10 s. Hypopneas were identified if airflow or respiratory effort decreased to <70% of baseline for at least 10 s, but did not fall so low as to qualify as an apnea. In most analyses reported here, only events that were associated with at least a 4% desaturation level (25) were included in the RDI, and these are presented in the text and tables. However, sensitivity analyses for definitions of RDI that were based on apneas and hypopneas that were defined using 2 and 3% destauration levels, with and without EEG arousal (26), are also included. The reliability of scoring of the RDI has been reported (27).

Because of their non-normal distribution, RDI variables were transformed using the formula log (RDI + 0.1), which achieved an approximately normal distribution. Back-transformed RDI values are presented for ease of interpretation. In some analyses, RDI was examined as a continuous variable, and in others it was divided into clinically defined cut-points (<5, 5 to <10, 10 to <15, and ≥15) and examined as a categorical variable.

***2*) Obstructive apnea index; central apnea index.** Apneas were further classified as obstructive if movement on either the chest or abdominal inductance channels was noted, or as central if no displacement was observed on both of these channels. Similar to the RDI, the obstructive apnea index (OAI) and central apnea index (CAI) presented in the tables were based on definitions that required events to be associated with a 4% desaturation. Sensitivity analyses were performed at different levels of desaturation (0–4%) and/or arousal. Both OAI and CAI data were highly skewed, with a considerable proportion of participants having zero values (OAI 27%, CAI 58%). These variables were therefore categorized as binary outcome variables. We report data for ≥3 events/h, but we also performed sensitivity analyses at a series of increasingly stringent cut-points for a positive outcome: ≥1, ≥2, ≥3, and ≥ 4 events/h of sleep.

***3*) Periodic breathing.** Periodic breathing (28) was noted if 10 consecutive min of a characteristic Cheyne Stokes breathing pattern was observed in sleep (i.e., a crescendo-decrescendo breathing pattern, or gradually increasing and decreasing respiratory effort, with typical cycle lengths of 30–60 s).

***4*) Percent sleep time <90% O_2 saturation (*T* < 90%).** The percent of total sleep time <90% O_2 saturation was recorded. Since a considerable proportion (25%) of the cohort spent no time with oxygen saturation levels <90%, participants were categorized according to whether they spent >5% and >10% of sleep time with oxygen levels <90%.

Sleep architecture

***5*) Sleep stages.** The percent of total sleep time spent in stage 1, stage 2, stages 3–4 (slow wave sleep), and in rapid eye movement (REM) sleep was scored according to standard criteria (29). Reliability of these scores has been reported (27). These outcomes were analyzed as continuous variables. To achieve approximate normality, the proportion of sleep time (*P*) in stages 1 and 3–4 were transformed according to the formula $-\log(-\log[P + 0.001])$. Back-transformed values are reported for ease of interpretation.

Definition of prevalent cardiovascular disease and diabetes

Definition of prevalent cardiovascular disease (CVD) was based on data reported by participants during the SHHS interview. These outcomes included history of hospitalized acute myocardial infarction, nonfatal coronary heart disease, stroke, angina, coronary artery bypass graft, and congestive heart failure. For the purposes

Table 1—*Baseline CVD risk factors among adults at risk for CVD. By diabetes status, Sleep Heart Health Study 1995–1998* (N = *4,872*)

Characteristic	Diabetes (n = 470)	No diabetes (n = 4,402)	Mean Difference (95% CI)*	P†
Age (years)	64.1 ± 10.0	62.1 ± 10.6	2.1 (1.1–3.1)	<0.001
Gender (% female)	54.0	55.7		0.49
Ethnicity (%)				
White	49.8	82.7		
African American	8.7	5.7		
American Indian	37.2	5.5		
Asian	0.9	1.5		
Hispanic	3.4	4.6		<0.001
BMI (kg/m^2)	31.3 ± 6.0	28.1 ± 5.1	3.2 (2.7–3.7)	<0.001
Waist circumference (cm)				
Males	106.5 ± 15.2	100.5 ± 14.3	6.0 (3.9–8.0)	<0.001
Females	107.6 ± 15.5	93.4 ± 15.1	14.2 (12.1–16.1)	<0.001
Neck circumference (cm)	39.5 ± 4.3	37.5 ± 4.2	2.4 (2.0–2.8)	<0.001
Total cholesterol (mg/dl)	197 ± 44	207 ± 38	−10 (−14 to −6)	<0.001
HDL cholesterol (mg/dl)	43 ± 13	52 ± 16	−9 (−10 to −7)	<0.001
Triglycerides (mg/dl)	188 ± 146	143 ± 96	44 (35–54)	<0.001
Ever a smoker (%)	53.3	52.3		0.66
Hypertension (%)	67.0	45.3		<0.001

Data are % for categorical variables and mean ± SD for continuous variables. *For continuous variables (mean among diabetes versus mean among non-diabetics). †P are for the χ^2 test of independence for categorical variables or the t test of differences in means for continuous variables.

of this report, CVD data were combined to form a single category representing individuals with prevalent CVD.

Since no blood was collected as part of the baseline SHHS exam, it was not possible to ascertain diabetes according to current clinical practice guidelines (30). Prevalent diabetes was therefore defined based on data on self-reported diabetes status and use of oral hypoglycemic medications and insulin that were collected during the SHHS interview.

Covariate data

Blood pressure measurements were collected before the PSG hook-up. Hypertension was defined as blood pressure ≥140/90 mmHg or as current treatment with antihypertensive medications (31). The medication inventory did not distinguish antihypertensive medications used for management of high blood pressure from those used for renal protection. Weight and neck circumferences were also measured during the home visit, and data on smoking status were collected by questionnaire. Data on height and lipoproteins were obtained from parent cohorts (11).

Statistical methods

The χ^2 and t tests were used to examine differences in proportions and means between categorical and continuous variables, respectively. These comparisons focused on differences in CVD risk factors, respiratory parameters, and sleep architecture measures between participants with and without diabetes. Descriptive analyses were supplemented by multivariable modeling in which diabetes was the primary predictor of interest. The objective of these analyses was to quantify the relationship between diabetes and various sleep measures independently of potential confounders.

Linear regression models were used to examine the relationship between diabetes and continuously distributed outcome variables, including log(RDI), and sleep stages. The logistic regression model was used to study the relationship between diabetes and the binary outcomes, including periodic breathing, CAI, OAI, and percent time with O_2 saturation <90%. In all multivariable analyses, age, sex, race, BMI, and neck circumference were forced into the model since these variables are known to be associated with both the occurrence of diabetes and SDB (4,32–34). Waist circumference was not included because of its high correlation with both BMI (Pearson correlation coefficient 0.74, $P < 0.0001$) and neck circumference (Pearson correlation coefficient 0.59, $P < 0.0001$).

Participants included in this report had complete data for age, race, diabetes status, BMI, and neck circumference. These inclusion criteria resulted in an analysis sample of 5,874 individuals (91.2% of the SHHS cohort). RDI data were available for the entire analysis sample. Calculation of CAI required both high-quality chest and abdominal effort data, and the OAI required high-quality airflow data. Among the 5,874 persons with complete covariate data, OAI data were available for 5,070 persons (86%) and CAI data were available for 4,462 persons (76%).

Examination of persons with prevalent CVD could generate misleading results about the association between diabetes and SDB since diabetes is common among people with CVD, and CVD is associated with some breathing disorders (35). Therefore, we conducted sensitivity analyses in which we first examined persons without CVD (n = 4,872) and then added participants with prevalent CVD (4,872 + 1,002 = 5,874).

RESULTS — Among 4,872 SHHS participants without CVD at baseline, diabetes was present in 470 individuals (9.6%). Diabetes prevalence increased to 11.8% with the addition of the 1,002 persons with prevalent CVD. Table 1 contrasts CVD risk factors between diabetic and nondiabetic participants among participants without CVD. Compared with those without reported diabetes, participants with diabetes were older (64.1 vs. 62.1 years), had lower HDL cholesterol levels (43 vs. 52 mg/dl), higher BMI (31.3 vs. 28.1 kg/m^2) and triglyceride levels (188 vs. 143 mg/dl), larger waist circumferences (males 106.5 vs. 100.5 cm, females 107.6 vs. 93.4 cm) and neck circumferences (39.5 vs. 37.5 cm), and were more likely to have hypertension (67 vs. 45%). No differences in the distribution of smoking or sex were observed between diabetic and nondiabetic individuals. Native Americans and African Americans were disproportionately represented among diabetic individuals compared with whites. The addition of the 1,002 persons with prevalent CVD

Table 2—*Baseline respiratory parameters and sleep architecture measures among adults at risk for CVD. By diabetes status, Sleep Heart Health Study 1995–1998* (N = *4,872*).

Characteristic	Diabetes (n = 470)	No diabetes (n = 4,402)	P*
RDI†	5.6	3.4	<0.001
<5 events/h	42.3	57.4	
5 to <10 events/h	21.3	17.9	
10 to <15 events/h	12.6	9.1	
≥ 15 events/h	23.8	15.6	<0.001
OAI (%)‡			
≥2 events/h	33.4	29.5	0.09
≥3 events/h	24.1	22.9	0.59
≥4 events/h	20.2	18.5	0.42
Sleep time <90% O_2 (%)			
>5%	20.5	13.0	<0.001
>10%	12.4	7.6	<0.001
Sleep stages (mean %)§			
1	5.5	4.7	<0.001
2	59.5	56.4	<0.001
3 and 4	12.0	15.7	<0.001
REM	18.7	20.1	<0.001
CAI (%)¶			
≥2 events/h	4.7	2.6	0.021
≥3 events/h	3.6	2.0	0.048
≥4 events/h	2.5	1.6	0.222
Periodic breathing (%)	3.8	1.8	0.002

Data are % for categorical variables and mean ± SD for continuous variables. *P values are for the χ^2 test of independence for categorical characteristics or the t test of differences in means for continuous characteristics. †Data are back transformed from [log(RDI + 0.1)] for 4% O_2 desaturation. Significance testing was performed on transformed data. ‡Data are for obstructive events with 4% O_2 desaturation or arousal. §Stages 1 and 3–4 data are back transformed from [−log(−log(P + 0.001))]. Significance testing was performed on transformed data. ¶Data are for events associated with 4% O_2 desaturation.

generally amplified differences in CVD risk factors between diabetic and nondiabetic individuals (data not shown).

It is shown in Table 2 that unadjusted geometric mean RDI was higher among diabetic compared with nondiabetic individuals (5.6 vs. 3.4 events/h). Consistent with differences in mean RDI, there was a significant difference in the distribution of diabetes across RDI categories, with proportionally more diabetic individuals in the higher categories. For example, 23.8% of diabetic subjects were in the RDI ≥15 group (a level consistent with SDB of moderate or more severity), compared with 15.6% of nondiabetic subjects. A higher unadjusted RDI was observed among diabetic individuals regardless of the use of alternative definitions of RDI (that required different degrees of oxygen desaturation and/or arousal to be linked with hypopneas and apneas included in any given RDI).

There was no difference in the frequency of obstructive breathing events between diabetic and nondiabetic participants, regardless of cut-point or definition used for identifying exclusively obstructive respiratory events (Table 2). However, a significantly larger proportion of diabetic participants spent >10% of sleep time with O_2 levels <90% (12.4 vs. 7.6%). Although the absolute differences in unadjusted means were small, diabetic participants spent more time in light sleep (stages 1 and 2) and less time in deeper sleep (stages 3 and 4, and REM).

The prevalence of central events was small—<5% for the cut-points examined in this report. However, a larger proportion of diabetic participants experienced central events, although a statistically significant difference was observed only for the cut-points of ≥2 and ≥3 events/h ($P < 0.05$, both). Consistent with the finding for central events overall, the prevalence of periodic breathing among diabetic participants was more than twice the prevalence among nondiabetic participants (3.8 vs. 1.8%, $P = 0.002$).

When analyses were repeated including the 1,002 individuals with prevalent CVD, these relationships persisted. However, differences between the diabetic and nondiabetic groups became more distinct with central events and periodic breathing ($P < 0.001$; data not shown).

Multivariable analyses were conducted in both analysis samples to determine whether unadjusted associations persisted after controlling for potential confounders. Linear regression analyses that controlled for age, sex, race, BMI, and neck circumference indicated no difference in adjusted geometric mean RDI between diabetic (3.7 events/h) and nondiabetic (3.6 events/h) participants (Table 3). However, BMI, age, and male sex were associated with increased RDI. The variables in these models accounted for 27% of the variance in RDI among people without CVD and 26% of RDI variance in the entire sample. These results were consistent across alternative definitions of RDI.

Similarly, no differences between diabetic and nondiabetic participants were

Table 3—*Relationship of diabetes to RDI* and sleep architecture† among participants free of CVD. Sleep Heart Health Study, 1995–1998.*

	RDI	% Stage 1	% Stage 2	% Stage 3–4	% REM
Diabetic	3.7 (3.25–4.14)	5.0 (4.7–5.4)	57.3 (56.2–58.4)	15.3 (14.1–16.6)	19.0 (18.4–19.6)
Nondiabetic	3.6 (3.42–3.69)	4.7 (4.6–4.8)	56.6 (56.3–56.9)	15.4 (15.0–15.7)	20.1 (19.9–20.3)
P	0.63	0.12	0.23	0.98	<0.001
Model R^2	0.27	0.08	0.13	0.19	0.03

Data are adjusted mean (95% CI). *Based on data from 4,872 participants. Means are adjusted for age, sex, race, BMI, and neck circumference. †Based on data from 4,762 participants. Means are adjusted for age, sex, race, BMI, and neck circumference.

Table 4—*Relation of diabetes to O_2 desaturation, central breathing disturbances, and periodic breathing**

	Outcome measure					
	RDI	Sleep time <90% saturation		Central events		Periodic breathing
	≥15 events/h	≥5%	≥10%	≥2 events/h	≥3 events/h	
Participants without CVD						
Odds ratio (95% CI)†	0.98 (0.75–1.27)	0.96 (0.73–1.27)	0.96 (0.69–1.35)	1.42 (0.80–2.55)	1.33 (0.69–2.57)	1.80 (1.02–3.15)
Participants with and without CVD						
Odds ratio (95% CI)	1.02 (0.82–1.26)	0.80 (0.72–1.13)	0.96 (0.74–1.26)	1.52 (0.99–2.33)	1.55 (0.97–2.47)	1.74 (1.16–2.61)

*Logistic regression models adjusted for age, sex, race, BMI, and neck circumference. †Diabetes vs. no diabetes.

observed in the adjusted proportion of sleep time in stages 1, 2, or 3 and 4, but a small reduction in the proportion of time spent in REM sleep was noted in the diabetic participants (19.0 vs. 20.1%, Table 3). The proportion of variability in sleep stages explained by these models ranged from 3% for REM sleep to 19% for stage 3–4. Repeating the analyses including the 1,002 participants with prevalent CVD did not alter these findings.

Logistic regression analyses (Table 4) showed no differences between diabetic subjects and nondiabetic subjects without CVD in the adjusted odds of having RDI ≥15 events/h (OR 0.98, 95% CI 0.75–1.27). Similarly, these analyses showed no effect of diabetes on the adjusted odds of spending ≥5 or ≥10% of sleep time <90% oxygen saturation (OR 0.96, 95% CI 0.73–1.27 for >5% sleep time and OR 0.96, 95% CI 0.69–1.35 for >10% of sleep time). Inclusion of participants with prevalent CVD did not alter these results.

A significantly increased odds of periodic breathing was observed among diabetic individuals without CVD compared with nondiabetic subjects (OR 1.80, 95% CI 1.02–3.15). Among participants without CVD, there was a suggestion of elevated odds associated with diabetes for the CAI, but the CIs overlapped 1.0 (OR 1.42, 95% CI 0.80–2.55 for ≥2 events/h and OR 1.33, 95% CI 0.69–2.57 for ≥3 events/h). Inclusion of the 1,002 participants with CVD strengthened associations with the CAI, although it still did not reach statistical significance. The increased adjusted odds of diabetes in relation to periodic breathing persisted when persons with CVD were included in the analysis (OR 1.74, 95% CI 1.16–2.62).

CONCLUSIONS — This report adds to a growing body of literature linking abnormalities of glucose metabolism with SDB. Most reports on this topic focus on a causal pathway in which SDB is hypothesized to increase the risk of developing diabetes (1,6,8–10,12,13). A key postulated link between SDB and diabetes in this pathway is the induction by SDB of insulin resistance, a well-known risk factor for diabetes (1,7,10,36).

Our data support the idea that diabetes is associated with SDB, but they also highlight the known role of obesity in this relationship. In unadjusted analysis of the RDI (an index of respiratory disturbance that contains both central and obstructive events), we observed consistent differences between diabetic subjects and nondiabetic subjects in the number of disturbances per hour of sleep, regardless of the definition of RDI examined. However, analyses that adjusted for obesity and other risk factors substantially reduced the association of diabetes with the RDI, indicating the importance of confounding in this relationship. Consistent with findings for RDI, we observed no adjusted difference in obstructive events between diabetic and nondiabetic participants. These findings are consistent with previous reports emphasizing the role of obesity in SDB prevalence among both diabetic and nondiabetic individuals (10,13). The increased occurrence of SDB among persons with diabetes, even if largely explained by obesity, is nevertheless important because SDB may exacerbate underlying CVD in this high-risk population. Thus, SDB may be a treatable CVD risk factor whose ascertainment could be of particular public health importance among people with diabetes.

Among all participants, the prevalence of periodic breathing was 5.4 and 2.5% in diabetic subjects and nondiabetic subjects, respectively—a prevalence OR of 2.23. Adjusted for confounders, this association was reduced to 1.74 but was statistically significant (1.16–2.61). In analyses of CVD-free participants, findings were essentially unchanged, despite the known relationship of certain manifestations of CVD with periodic breathing (adjusted OR 1.80, 95% CI 1.02–3.15). It is important to emphasize that the definition of periodic breathing in this study was conservative (10 min of the characteristic crescendo-decrescendo pattern), observed in sleep (usually in non-REM, and apart from sleep onset). This definition was chosen to maximize the specificity of identifying participants who exhibited periodic breathing. It is possible that the association of diabetes and periodicity among people with CVD may have been due to confounding by underlying congestive heart failure (35,37–39). However, the persistence of this observation in those without CVD is a unique finding that may suggest some unique etiology of periodic breathing among diabetic individuals.

In contrast to findings for central apnea, we observed no differences between diabetic and nondiabetic participants in indexes based exclusively or predominantly on obstructive events once obesity was accounted for. This relates to the strong confounding effect of obesity. We also observed no meaningful differences in sleep architecture. Although we noted a difference in adjusted time in REM sleep between diabetic subjects and nondiabetic subjects, this difference (1.1%), while statistically significant due to the large sample size, is not clinically meaningful. Similarly, adjusted regression analyses showed no differences in RDI between diabetic and nondiabetic participants. Thus, our initial observation of differences in mean RDI between diabetic and nondiabetic participants was explained by differences in common risk factors between the groups, but this was not the case for central events.

Consistent with the increased frequency of periodic breathing among persons with diabetes was the suggestion of an increased occurrence of central events among diabetic subjects, a finding we initially observed both in the presence and absence of CVD and across all categories of CAI. However, the relationship between diabetes and CAI diminished below statistical significance following multiple adjustments, although the lower boundary for the CIs was 0.99 and 0.97 in some cases. The lack of statistical significance of diabetes in relation to CAI may relate to the small number of individuals with central events and to the potential misclassification of central events that may occur when using traditional noninvasive methods of distinguishing central from obstructive events (40), and because of the more limited power to detect effects in the subsample with high-quality data for both abdominal and thorax band signals. Thus, the combination of low power and misclassification of diabetes may have contributed to the absence of statistically significant associations.

Taken together, these data lead us to propose an additional (not alternate) role for diabetes in relation to SDB and CVD—our data are consistent with the hypothesis that instability of breathing during sleep, particularly associated with central breathing abnormalities, may result in part from dysfunction of the autonomic nervous system, a common complication of diabetes.

This hypothesized relationship places diabetes as a risk factor for certain types of breathing abnormalities, in addition to the converse, as published recently (1,6,8–10,12,13). We therefore propose that diabetes may be both a cause and a result of SDB. The hypothesis that autonomic neuropathy may increase risk of breathing abnormalities is supported by a report showing that sleep apnea is more common in diabetic individuals with autonomic neuropathy than in those without (14) and others suggesting a role for autonomic neuropathy in central control of respiration (18,19).

At least two mechanisms may link autonomic neuropathy with a periodic (Cheyne Stokes) breathing pattern. This breathing pattern is characterized by instability in respiratory control with alternating periods of hyperventilation and hypoventilation, produced by a number of factors that disturb normal feedback control mechanisms. First, autonomic neuropathy may disturb underlying respiratory control by altering central chemoreceptor gain via disinhibiting effects contributing to the ventilatory overshoot observed. Second, impaired cardiovascular function (diminished heart rate variability and left ventricular dysfunction) common in diabetic neuropathy may prolong circulatory time and cause a delay in feedback loops involving CO_2 and/or O_2 chemoreceptors in the brain and heart, respectively. This hypothesis is supported by a report showing that increasing heart rate and cardiac output through atrial pacing reduced the number of central apneas in 15 people with symptomatic bradycardia and low ejection fraction (41). Although this study could not link autonomic dysfunction with central sleep apnea, evidence from a rare, progressive neurodegenerative disorder supports this postulated relationship. Shy-Drager Syndrome is characterized by severe orthostatic hypotension, diminished thermoregulation, impotence, and abnormal gastric function, all common features of diabetic autonomic neuropathy (42). Sleep apnea is also common in Shy-Drager, particularly central sleep apnea, and abnormalities of normal respiratory oscillation and circadian variation in blood pressure have been reported (43–45).

Several methodologic features of this study warrant comment. To thoroughly examine the relation of diabetes to various features of SDB, we performed sensitivity analyses by including and excluding persons with prevalent CVD. The latter sample was designed to reduce *1*) confounding of risk factors such as obesity that are common to both diabetes and SDB; *2*) the possibility that important SDB risk factors such as obesity were not influenced by a diagnosis of CVD; and *3*) the effect of the known relationship between heart failure or left ventricular dysfunction and periodic breathing. Results of these analyses were consistent with respect to associations between diabetes and various sleep measures.

It is important to stress that in the SHHS, diabetes was ascertained from data provided by the parent studies. Most of these data were self-report of diabetes as determined during parent study interviews before the baseline examination of SHHS. As a result, such factors as *1*) frequency of parent study examination cycles, *2*) whether the parent study collected biological samples that would influence a participant's response to an interview question, and *3*) the interval between the last parent study examination and the baseline examination of SHHS would all influence self-reported diabetes in SHHS. To address the possibility that a "parent study effect" was driving associations between diabetes and the SDB measures examined here, we repeated all analyses including dummy variables representing the parent studies. Adjustment for study site had no material effect on the results.

Another issue related to self-report of diabetes is misclassification of diabetes status. It is well known that self-report of diabetes may underestimate the true prevalence of diabetes by as much as 50% (46). Thus, it is possible the 692 persons with reported diabetes may have represented only half of the diabetic individuals in the SHHS cohort. However, additional cases identified by blood chemistry alone would likely be newer and/or milder cases with less neuropathy.

Lastly, it should be noted that measures such as heart rate variability or postural hypotension would have allowed a more direct examination of the postulated mechanisms underlying the causal pathways underpinning the hypotheses in this report. Without data providing information on the presence and/or severity of autonomic function, our hypothesis of a role of diabetic autonomic neuropathy as a risk factor for abnormalities of central respiration in diabetes remains speculative. Given this limitation, it is important to note that a well-known, population-based study of neuropathy showed that among adults with established diabetes, the prevalence of diabetic neuropathy was 47% (47). That nearly one-half of people with established diabetes have diabetic neuropathy supports our hypothesis for a role of this diabetic complication in sleep apnea. However, only a future study with PSG data, a large number of diabetic individuals, and measures of autonomic function will be able to directly address this hypothesis.

In summary, baseline data from the SHHS indicate no cross-sectional differences in RDI, sleep stages, or obstructive apnea between diabetic and nondiabetic individuals. Consistent, but nonstatistically significant, differences were observed between diabetic and nondiabetic

persons in prevalence of central apnea, and a significant difference was observed between the groups in the prevalence of periodic breathing. It is not clear whether central sleep disturbances may be caused by diabetes or whether they may specifically relate to effects of autonomic neuropathy or other diabetic complications on control of respiration. Future research from the SHHS examining the incidence of central apnea in relation to baseline diabetes will help answer this question.

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References

1. Grunstein RR, Stenlof K, Hedner J, Sjostrom L: Impact of obstructive sleep apnea and sleepiness on metabolic and cardiovascular risk factors in the Swedish Obese Subjects (SOS) Study. *Int J Obes Relat Metab Disord* 19:410–418, 1995
2. Kiley JL, McNicholas WT: Cardiovascular risk factors in patients with obstructive sleep apnoea syndrome. *Eur Respir J* 16: 128–133, 2000
3. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG: Association of sleep-disordered breathing, sleep apnea and hypertension in a large, community-based study: Sleep Heart Health Study. *JAMA* 283: 1029–1036, 2000
4. Cowie CC, Harris MI: Physical and metabolic characteristics of persons with diabetes. In *Diabetes In America* (2nd Edition). National Institute of Diabetes, Digestive and Kidney Diseases. National Institutes of Health, Bethesda, MD, 1995 (NIH publ. no. 95-1468)
5. Wingard DL, Barrett-Connoer E: Heart disease in diabetes. In *Diabetes In America* (2nd Edition). National Institute of Diabetes, Digestive and Kidney Diseases. National Institutes of Health, Bethesda, MD, 1995 (NIH publ. no. 95-1468)
6. Spiegel K, Leproult R, Van Cauter E: Impact of sleep debt on metabolic and endocrine function. *Lancet* 354:1435–1439, 1999
7. Strohl KP, Novak RD, Singer W, Cahan C, Boehm KD, Denko CW, Hoffstein VS: Insulin levels, blood pressure and sleep apnea. *Sleep* 17:614–618, 1994
8. Tiihonen M, Partinen M, Narvanen S: The severity of obstructive sleep apnea is associated with insulin resistance. *J Sleep Res* 2:56–61, 1993
9. Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP: Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercyokinemia. *J Clin Endocrinol Metab* 85:1151–1158, 2000
10. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL: Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am J Respir Crit Care Med* 165:677–682, 2002
11. NewmanAB, Nieto FJ, Guidry U, Lind BK, Redline S, Shahar E, Pickering TG, Quan SF: Relation of sleep-disordered breathing to cardiovascular disease risk factors: the Sleep Heart Health Study. *A J Epidemiol* 154:50–59, 2001
12. Elmasry A, Janson C, Lindberg E, Gislason T, Tageldin MA, Boman G: The role of habitual snoring and obesity in the development of diabetes: a 10-year follow-up study in a male population. *J Intern Med* 248:13–20, 2000
13. Al-Delaimy WK, Manson JE, Willett WC, Stampfer MJ, JU FB: Snoring as a risk factor for type II diabetes mellitus: a prospective study. *Am J Epidemiol* 155:387–393, 2002
14. Ficker JH, Dertinger SH, Siegfried W, Koning HJ, Pentz M, Sailer D, Katalinic A, Hahn EG: Obstructive sleep apnoea and diabetes mellitus: the role of cardiovascular autonomic neuropathy. *Eur Respir J* 11:14–19, 1998
15. Ewing DJ, Neilson JM, Shapiro CM, Stewart JA, Reid W: Twenty four hour heart rate variability: effects of posture, sleep, and time of day in health controls and comparison with bedside tests of autonomic function in diabetic patients. *Br Heart J* 65:239–244, 1991
16. Bauer T, Ewig S, Schafer H, Jelen E, Omran J, Luderitz B: Heart rate variability in patients with sleep-related breathing disorders. *Cardiology* 87:492–496, 1996
17. Page MM, Watkins PJ: Cardiopulmonary arrest and diabetic autonomic neuropathy. *Lancet* I:14–16, 1978
18. Tantucci C, Scionti L, Bottini P, Dottorini ML, Puxeddu E, Casucci G, Sorbini CA: Influence of autonomic neuropathy of different severities on the hypercapnic drive to breathing in diabetic patients. *Chest* 112:145–153, 1997
19. Rees PJ, Cochrane GM, Prior JG, Clark TJH: Sleep apnea in diabetic patients with autonomic neuropathy. *J R Soc Med* 74: 192–195, 1981
20. Neumann C, Martinez D, Schmid H: Nocturnal oxygen desaturation in diabetic patients with severe autonomic neuroapthy. *Diabetes Res Clin Pract* 28:97–102, 1995
21. Sobotka PA, Liss HP, Vinik AI: Impaired hypoxic ventilatory drive in diabetic patients with autonomic neuropathy. *J Clin Endocrinol Metab* 62:658–663, 1986
22. Quan SF, Howard BV, Iber C, Kiley JP, Nieto FJ, O'Connor GT, Rapoport DM, Redline S, Robbins J, Samet JM, Wahl PW: The Sleep Heart Health Study: design rationale and methods. *Sleep* 20: 1077–1085, 1997
23. Redline S, Sanders MH, Lind BK, Quan SF, Iber C, Gottlieb DJ, Bonekat WH, Rapoport DM, Smith PL, Kiley JP: Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. *Sleep* 21:759–767, 1998
24. http://ins1.jhsph.edu/Research/Centers/CCT/shhs/. Accessed November 2002.
25. American Sleep Disorders Association: EEG arousals: scoring rules and examples [ASDA Report]. *Sleep* 15:173–184, 1992
26. Redline S, Kapur VK, Sanders MH, Quan SF, Gottleib DJ, Rapoport DM, Bonekat WH, Smith PL, Kiley JP, Iber C: Effects of varying approaches for identifying respiratory disturbances on sleep apnea assessment. *Am J Respir Crit Care Med* 161:369–374, 2000
27. Whitney CW, Gottleib DJ, Redline S, Norman RG, Dodge RR, Shahar E, Surovec S, Nieto FJ: Reliability of scoring disturbance indices and sleep staging. *Sleep* 21:749–757, 1998
28. Ward M: Periodic respiration: a short historical note. *Ann Coll Surg Engl* 52:330–334, 1973
29. Rechtschaffen A, Kales A, Eds: *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human*

Subjects. BIS/BRI University of California, Los Angeles, 1968
30. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 25 (Suppl. 1):S5–S20, 2002
31. National High Blood Pressure Education Program: *The Fifth Report of the Joint National Committee in Detection, Evaluation, and Treatment of High Blood Pressure*. Bethesda, MD, U.S. Govt. Printing Office, 1993 (NIH publ. no. 93–1088)
32. Partinen M: Epidemiology of obstructive sleep apnea syndrome. *Curr Opin Pulm Med* 1:482–487, 1995
33. Davies RJ, Stradling JR: The relationship betweeen neck circumference, radiographic pharyngeal anatomy, and the obstructive sleep apnoea syndrome. *Eur Respr J* 3:509–514, 1990
34. Levinson PD, McGarvey St, Carlisle CC, Eveloff Se, Herbert PN, Millman RP: Adiposity and cardiovascular risk factors in men with obstructive sleep apnea. *Chest* 103:1336–1342, 1993
35. Javaheri S: A mechanism of central sleep apnea in patients with heart failure. *N Engl J Med* 341:949–954, 1999
36. Ip MSM, Lam B, Ng MMT, Lam WK, Tsang KWT, Lam KS: Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med* 165:670–676, 2002
37. Findley LJ, Zwillich C, Ancoli-Israel S, Kripke K, Tisi G, Moser KM: Cheyne-Stokes breathing during sleep in patients with left ventricular heart failure. *South Med J* 78:11–15, 1985
38. Rees PJ, Clart TSH: Paroxysmal nocturnal dyspnea and periodic respiration. *Lancet* 2:1315–1317, 1979
39. Javaheri S, Parker TJ, Wexler L, Michaels SE, Stanberry E, Nishyama H, Roselle GA: Occult sleep-disordered breathing in stable congestive heart failure. *Ann Intern Med* 122:487–492, 1995
40. Flemons WW, Buysse D, Redline S, Pack M, Strohl K, Wheatley J, Young T, Douglas N, Levy P, McNicholas W, Fleetham J, White D, Schmidt-Nowarra W, Carley D, Romaniuk J: Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research: the Report of an American Academy of Sleep Medicine Task Force. *Sleep* 22:533–700, 1999
41. Garrigue S, Bordier P, Jais P, Shah DC, Hocini M, Raherison C, DeLara MT, Haissaguerre M, Clementy J: Benefit of atrial pacing in sleep apnea syndrome. *N Engl J Med* 346:404–412, 2002
42. Shy GM, Drager GA: A neurological syndrome associated with orthostatic hypotension: a clinical-pathological study. *Arch Neurol* 2:511–527, 1960
43. Guilleminault C, Briskin JG, Greenfiled MS, Silvestri R: The impact of autonomic nervous system dysfunction on breathing during sleep. *Sleep* 4:263–278, 1981
44. Chester CS, Gottfried SB, Cameron DI, Strohl KP: Pathologic findings in a patient with Shy-Drager and alveolar hypoventilatory syndromes. *Chest* 94:212–214, 1988
45. Imai Y, Abe K, Munakata M, Sakuma H, Hashimoto J, Imai K, Sekino H, Yoshinaga K: Circadian blood pressure variations under different pathophysiologic conditions (Review Article). *J Hypertens Suppl* 8:S125–S132, 1990
46. Harris MI, Hadden WC, Knowler WC, Bennett PH: Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in U.S. population aged 20–74 yr. *Diabetes* 36:523–534, 1987
47. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, Wilson DM, O'Brien PC, Melton LJ III, Service FJ: The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology* 43:817–824, 1993