

Associations of sleep disturbance and duration with metabolic risk factors in obese persons with type 2 diabetes: data from the Sleep AHEAD Study

Marie-Pierre St-Onge¹

Gary Zammit²

David M Reboussin³

Samuel T Kuna⁴

Mark H Sanders⁸

Richard Millman⁶

Anne B Newman⁵

Thomas A Wadden⁴

Rena R Wing⁶

F Xavier Pi-Sunyer¹

Gary D Foster⁷

Sleep AHEAD Research

Group*

¹New York Obesity Research Center, St Luke's/Roosevelt Hospital, New York, NY, USA; ²Clinilabs, New York, NY, USA;

³Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA; ⁴Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA; ⁵Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA, USA; ⁶Department of Psychiatry and Human Behavior, Brown University, Providence, RI, USA; ⁷Center for Obesity Research and Education, Temple University, Philadelphia, PA, USA;

⁸Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh, PA, USA

*A full list of the members of the Sleep AHEAD Research Group is available in an online appendix

Correspondence: Marie-Pierre St-Onge
New York Obesity Research Center,
St Luke's/Roosevelt Hospital, 1090
Amsterdam Avenue, Suite 14D,
New York, NY 10025, USA
Tel +1 212 523 3564
Fax +1 212 523 3571
Email ms2554@columbia.edu

Purpose: Some studies have found an association between sleep disturbances and metabolic risk, but none has examined this association in individuals with type 2 diabetes. The objective of this study was to determine the relationship between sleep disturbances and metabolic risk factors in obese patients with type 2 diabetes.

Patients and methods: This study was a cross-sectional examination of the relationship between sleep parameters (apnea/hypopnea index [AHI], time spent in various sleep stages) and metabolic risk markers (fasting glucose, hemoglobin A_{1c}, lipids) using baseline data of the Sleep AHEAD cohort. Subjects (n = 305) were participants in Sleep AHEAD (Action for Health in Diabetes), a four-center ancillary study of the Look AHEAD study, a 16-center clinical trial of overweight and obese participants with type 2 diabetes, designed to assess the long-term effects of an intensive lifestyle intervention on cardiovascular events. All participants underwent one night of in-home polysomnography and provided a fasting blood sample. Regression analyses estimated the relationship between sleep variables and metabolic risk factors. Models were adjusted for study center, age, sex, race/ethnicity, waist circumference, smoking, alcohol intake, diabetes duration, and relevant medications.

Results: Of 60 associations tested, only one was significant: fasting glucose was associated with sleep efficiency (estimate $-0.53 \pm$ [standard error] 0.26, $P = 0.041$). No associations were found between any of the sleep variables and lipid profile or hemoglobin A_{1c}.

Conclusions: The present data show only weak associations between select sleep variables and metabolic risk factors and do not provide strong support for a role of sleep on metabolic abnormalities in obese patients with type 2 diabetes.

Keywords: obesity, obstructive sleep apnea, metabolic risk, sleep, diabetes

Introduction

Recent studies have suggested that sleep duration, as well as sleep disturbances, may play a role in the development of metabolic abnormalities. Chaput et al¹ reported that short or long sleep duration increased the risk for incident diabetes over a 6-year follow-up period in the Quebec Family Study. Individuals with short sleep duration, defined as those sleeping ≤ 6 hours/night, also had higher fasting plasma insulin and insulin resistance, assessed by the homeostatic model (HOMA-IR), than average sleepers, defined as those sleeping 7–8 hours/night.¹ A similar association between sleep duration and incident diabetes was reported from the Insulin Resistance and Atherosclerosis Study.² In the Sleep Heart Health Study,³ a relationship between sleep duration and impaired glucose tolerance and diabetes was also observed. Data from the Hordaland Health Study suggest a relationship between short sleep duration and

elevated total cholesterol and triglyceride, and lower high-density lipoprotein (HDL) cholesterol levels.⁴

Studies of sleep restriction in healthy adults also support a role for sleep duration in the etiology of metabolic disturbances. For example, reductions in sleep by approximately 2 hours/night increased 2-hour glucose and area under the curve for glucose during a 3-hour oral glucose tolerance test,⁵ as well as reduced insulin sensitivity, glucose tolerance, and the disposition index,⁶ relative to longer sleep duration. Sleep restriction has also been shown to increase total and low-density lipoprotein (LDL) cholesterol in postmenopausal women.⁷

Sleep disorders such as sleep apnea have also been associated with increased risk of incident diabetes.⁸ In a convenience sample of individuals with type 2 diabetes presenting at a primary care and endocrinology clinic, those with severe obstructive sleep apnea (OSA) had more diabetes complications and poorer glycemic control than individuals with less severe OSA.⁹ Intervention studies have also shown that suppression of slow-wave sleep for three nights reduces insulin sensitivity with reductions in glucose disposition index and glucose tolerance compared to undisturbed sleep in healthy, lean young men and women.¹⁰ Studies have also suggested that the presence of OSA is associated with higher odds of metabolic syndrome¹¹ and higher levels of metabolic syndrome indicators (blood pressure, fasting glucose, triglycerides) than those without OSA.^{11,12} In the São Paulo Epidemiologic Sleep Study, severity of OSA was significantly associated with impaired fasting glucose and HOMA, such that those with moderate OSA were 1.67 times more likely to have impaired fasting glucose or type 2 diabetes, and those with moderate-to-severe OSA were twice as likely to have insulin resistance than participants without OSA.¹³

Epidemiological and clinical studies in healthy individuals point to a link between sleep duration and disturbances and diabetes risk. However, Björkelund et al¹⁴ found no association between sleep duration, complaints, or medications and 32-year incidence of diabetes in a population study of women, and there was no relationship between sleep duration and HOMA-IR in the Wisconsin Sleep Cohort Study.¹⁵ In clinical studies, Bomya-Westphal et al¹⁶ found no effect of sleep restriction on glucose, insulin, and insulin sensitivity in healthy women. It has been proposed that there may be a threshold of minimum sleep required to maintain normal glucose control and that clinical studies showing the greatest difference in sleep duration between test periods show an effect of sleep on glucose metabolism.^{17,18} It is also possible

that the measurements used to assess insulin resistance were not sensitive enough to detect effects of sleep duration on this marker of diabetes risk.

The present study used data from the Sleep AHEAD (Action for Health in Diabetes) cohort to determine whether sleep duration and disturbances were associated with metabolic abnormalities in obese, type 2 diabetic individuals. Based on epidemiological findings, it was hypothesized that shorter sleep duration and higher AHI would both be associated with a more adverse metabolic profile. Exploratory analyses were performed to determine if components of the sleep architecture would be specifically related to metabolic risk factors.

Methods

Participants

Participants for this study were enrolled in the Sleep AHEAD Study, whose purpose is to examine the effects of weight loss on sleep-disordered breathing in obese patients with OSA and type 2 diabetes over a 4-year period. Although Sleep AHEAD is a longitudinal study, the present study reports on baseline, cross-sectional data. Sleep AHEAD is a four-center, ancillary study of Look AHEAD, a 16-center clinical trial investigating the long-term health impact of an intensive lifestyle intervention in 5145 overweight or obese adults with type 2 diabetes. The details of Look AHEAD's design,¹⁹ participant characteristics at baseline,²⁰ and intervention²¹ (including inclusion and exclusion criteria) have been described elsewhere. Primary inclusion criteria for Look AHEAD were age 45–75 years, body mass index (BMI) ≥ 25 kg/m² (≥ 27 if currently taking insulin), physician-verified type 2 diabetes, hemoglobin A_{1c} (HbA_{1c}) $< 11\%$, and arterial pressure < 160 mmHg systolic and < 100 mmHg diastolic. In addition to Look AHEAD criteria, exclusion criteria for Sleep AHEAD were surgical or medical treatment for OSA. Those with previously diagnosed but untreated OSA were eligible. In the Sleep AHEAD population, 86.6% of participants had mild to severe OSA.²²

Procedures

Sleep AHEAD participants were recruited at four of the Look AHEAD sites: University of Pennsylvania (Philadelphia, PA), University of Pittsburgh (Pittsburgh, PA), St Luke's/Roosevelt Hospital (Columbia University, New York, NY), and Brown University (Providence, RI). The study was approved by the institutional review boards at each of the participating sites, and all participants provided written informed consent. At the second Look AHEAD screening visit, a research assistant informed subjects about Sleep AHEAD.

Interested participants then consented to a screening to assess eligibility. Each Sleep AHEAD site enrolled participants until its target levels (approximately 75 per site or 300 across sites) were achieved. Total enrollment in Sleep AHEAD was 306.

Polysomnography

Baseline polysomnograms were performed prior to any intervention from the Look AHEAD study and were done in the participants' home with a portable monitor (PS2; Compumedics, Abbotsford, Australia) using techniques similar to those developed for the Sleep Heart Health Study.²³ The participants were prepared for recording in their homes by two sleep technologists. Participants were instructed to go to bed at their regular time, and the monitors were programmed to start recording 1 hour earlier. Technologists returned to the participants' homes the following morning to remove the sensors and retrieve the monitors. The initial failure rate for baseline Sleep AHEAD polysomnography (PSG) recordings was 7.2% (22 of 306). Among the 22 participants with failed studies, twelve had successful repeat testing, nine declined further testing, and one failed testing on the second attempt, resulting in an actual failure rate of 3.3% (ten of 306), which is similar to the 5.3% failure rate found in the Sleep Heart Health Study.²⁴

All polysomnograms were scored manually with the aid of computer software by the same registered PSG technologist. The scoring of sleep stages, apneas, and hypopneas was performed in accordance with the criteria of the American Academy of Sleep Medicine criteria, using a 4% oxygen desaturation cutoff to score hypopneas.^{25,26} Intrascorer reliability was determined by having the blinded scorer rescore 32 randomly chosen Sleep AHEAD polysomnograms. The intraclass correlation coefficient for AHI was 0.89. A value >0.80 is considered excellent.²⁷ Sleep variables considered in this study included: total sleep time, percent time spent in each sleep stage, sleep efficiency (% time asleep), arousal index (average number of arousals per hour of sleep), average desaturation/apnea-hypopnea (percent change in Hb oxygen saturation), number of wake episodes, and AHI.

The following data (dependent variables) were obtained from the Look AHEAD study files: HbA_{1c}, glucose, triglycerides, total cholesterol, LDL-cholesterol, and HDL-cholesterol. These tests were obtained at the time that subjects entered the Look AHEAD study. All metabolic variables were measured from fasting blood samples.¹⁹

For the statistical analysis, an indicator variable was used for whether or not the participant was taking a diabetes or

lipid-lowering medication. Six dependent variables and ten sleep parameters were analyzed. For each dependent variable, ten linear regression models were fit, one for each sleep parameter separately. Each model was adjusted for study site, age, sex, race/ethnicity, waist circumference, smoking (coded as never, past, present), alcohol, and diabetes duration. In addition, HbA_{1c} and fasting glucose were adjusted for use of diabetes medication, and lipid variables (total, LDL-, and HDL-cholesterol, and triglycerides) were adjusted for use of lipid-lowering medication. Medication use was assessed at home visits. The residuals and measures of collinearity were also checked for all 60 models; there was no indication that modeling assumptions were violated. Results are reported as estimated slope coefficients \pm standard error for each regression. Results were not adjusted for multiple comparisons. A total of 305 participants were included in the analysis; one participant with central sleep apnea (>50% of apneas as central apneas) was excluded.

Results

On average, participants had a BMI of approximately 36.5 ± 0.3 kg/m² and an age of 61 ± 0.4 years. Study participants slept on average 5.96 ± 1.21 hours/night and had an AHI of 29.8 ± 19.4 events/hour. Diabetes duration was 7.3 ± 0.4 years. Except for HDL-cholesterol, baseline metabolic variables were elevated (Table 1).

There was no significant independent association between any of the sleep variables and HbA_{1c}, total cholesterol, LDL-cholesterol, or HDL-cholesterol (Table 2). There was a significant inverse association between fasting plasma glucose and sleep efficiency (-0.53 ± 0.26 , $P = 0.041$).

Table 1 Participant characteristics

Characteristics	Mean (SE)
Sex, male/female	122/183
Race, AA/C/H/O	58/223/10/14
Age, years	61.3 (0.4)
Waist circumference, cm	115.0 (0.7)
Body mass index, kg/m ²	36.5 (0.3)
Use of diabetes medication, Y/N ^a	264/40
Use of lipid-lowering medication, Y/N ^a	161/143
Hemoglobin A _{1c} , %	7.22 (0.06)
Fasting plasma glucose, mg/dL	153.6 (2.6)
Total cholesterol, mg/dL	192.4 (2.2)
LDL-cholesterol, mg/dL	114.6 (1.8)
HDL-cholesterol, mg/dL	45.4 (0.7)
Triglycerides, mg/dL	163.6 (5.5)

Note: ^aData missing for one person.

Abbreviations: SE, standard error; AA, African-American; C, Caucasian; H, Hispanic; O, other; LDL, low-density lipid; HDL, high-density lipid.

Table 2 Association of metabolic variables and sleep parameters

Dependent variables	Sleep parameter	Estimate	Standard error	P-value
Hemoglobin A _{1c} ^a	Sleep, hours	0.053	0.055	0.340
	Sleep efficiency, % time in bed as sleeping	-0.0039	0.0060	0.512
	% time in stage 1	0.31	0.42	0.457
	% time in stage 2	-0.22	0.43	0.607
	% time in delta	-0.94	1.28	0.464
	% time in REM	-0.040	0.83	0.961
	Arousal index	0.0048	0.0048	0.325
	Average desaturation/apnea-hypopnea	-0.052	0.15	0.731
	Number of wake episodes	0.0055	0.0071	0.441
	Apnea/hypopnea index	-0.0017	0.0035	0.625
Fasting plasma	Sleep, hours	-0.92	2.43	0.706
Glucose, mg/dL ^a	Sleep efficiency, % time in bed as sleeping	-0.53	0.26	0.041
	% time in stage 1	15.76	17.96	0.381
	% time in stage 2	-11.70	18.70	0.532
	% time in delta	11.16	55.32	0.840
	% time in REM	-25.56	35.70	0.474
	Arousal index	0.13	0.21	0.520
	Average desaturation/apnea-hypopnea	3.96	6.50	0.543
	Number of wake episodes	0.25	0.31	0.420
	Apnea/hypopnea index	-0.15	0.15	0.326
	Total cholesterol, mg/dL ^b	Sleep, hours	1.43	1.90
Sleep efficiency, % time in bed as sleeping		-0.030	0.20	0.882
% time in stage 1		-2.03	14.04	0.885
% time in stage 2		12.13	14.62	0.407
% time in delta		-23.57	43.37	0.587
% time in REM		-26.07	27.92	0.351
Arousal index		-0.098	0.16	0.551
Average desaturation/apnea-hypopnea		-8.53	5.07	0.093
Number of wake episodes		-0.040	0.24	0.867
Apnea/hypopnea index		0.23	0.12	0.050
LDL-cholesterol, mg/dL ^b	Sleep, hours	0.25	1.51	0.869
	Sleep efficiency, % time in bed as sleeping	-0.076	0.16	0.636
	% time in stage 1	-3.92	11.11	0.724
	% time in stage 2	7.85	11.57	0.498
	% time in delta	9.40	34.34	0.784
	% time in REM	-16.73	22.10	0.450
	Arousal index	-0.11	0.13	0.400
	Average desaturation/apnea-hypopnea	-4.78	4.02	0.236
	Number of wake episodes	-0.093	0.19	0.625
	Apnea/hypopnea index	0.10	0.093	0.260
HDL-cholesterol, mg/dL ^b	Sleep, hours	1.09	0.60	0.070
	Sleep efficiency, % time in bed as sleeping	0.065	0.064	0.311
	% time in stage 1	-5.80	4.41	0.190
	% time in stage 2	6.94	4.60	0.132
	% time in delta	-1.81	13.70	0.895
	% time in REM	-1.63	8.83	0.853
	Arousal index	-0.044	0.052	0.395
	Average desaturation/apnea-hypopnea	-1.99	1.60	0.216
	Number of wake episodes	0.016	0.076	0.837
	Apnea/hypopnea index	0.0060	0.037	0.987
Log triglycerides ^b	Sleep, hours	0.0039	0.027	0.882
	Sleep efficiency, % time in bed as sleeping	-0.0017	0.0028	0.539
	% time in stage 1	0.24	0.20	0.215
	% time in stage 2	-0.050	0.20	0.806
	% time in delta	-1.03	0.60	0.088

(Continued)

Table 2 (Continued)

Dependent variables	Sleep parameter	Estimate	Standard error	P-value
	% time in REM	-0.35	0.39	0.372
	Arousal index	0.0012	0.0023	0.614
	Average desaturation/apnea-hypopnea	-0.049	0.071	0.489
	Number of wake episodes	0.0025	0.0033	0.451
	Apnea/hypopnea index	0.0026	0.0016	0.111

Notes: Each model was adjusted for site, age, sex, race/ethnicity, waist circumference, smoking, alcohol, and diabetes duration, plus an indicator for glucose-^a or lipid-lowering^b medication use (assessed at home visits), as appropriate.

Abbreviations: REM, rapid eye movement; LDL, low-density lipid; HDL, high-density lipid.

Discussion

This is one of few studies to examine the relationship between sleep architecture, assessed using PSG, and metabolic risk factors, specifically in obese patients with type 2 diabetes. It was hypothesized that shorter sleep duration, components of sleep architecture, and higher AHI would be associated with a more adverse metabolic profile. Although there was a significant association between sleep efficiency and fasting plasma glucose in the present study, the data do not support a relationship between sleep or AHI and metabolic risk in obese patients with type 2 diabetes. The weak association that was observed was one of many different associations tested (60 tests of associations) and may have occurred due to type 2 error. Moreover, as our analyses were exploratory, we did not adjust for multiple comparisons, and type 1 errors could be larger than stated. Additional studies are needed to provide more definitive conclusions concerning the relationship between sleep and metabolic risk in diabetics.

Study participants were obese and had diabetes. Previous studies examining the association between self-reported sleep duration and metabolic risk factors have found that short sleep increases the risk of incident diabetes.^{1,2} However, these studies included a wide range of participants with and without diabetes or insulin resistance at baseline and did not assess sleep-disordered breathing. It is possible that sleep characteristics play a role in the development of diabetes and cardiovascular disease, but are not important predictors of the severity of other metabolic risk factors once diabetes is established. Moreover, study participants had a small range of HbA_{1c} values (7.22% ± 1.07%). In a previous study with participants with a wider range of HbA_{1c} (7.7% ± 1.8%), HbA_{1c} was significantly associated with severity of OSA in diabetic patients.⁹

Previous studies have found that patients with OSA have higher glucose and triglycerides,^{15,28} and Drager et al¹² also found higher total cholesterol and LDL-cholesterol in OSA patients compared to patients without OSA. The present data did not show an association between AHI and any of

the metabolic risk factors measured in this study. Of note is that participants of this study all had type 2 diabetes, whereas none of the participants in the study by Drager et al,¹² 24% of the OSA patients, and 11% of patients without OSA had type 2 diabetes in the study by Gasa et al.¹¹ Sharma et al²⁸ also found that metabolic risk factors were not different between obese individuals with OSA and obese controls without OSA, both groups being free of diabetes. Furthermore, in the Sleep Heart Health Study, while AHI was associated with prevalent cardiovascular disease, there was no relationship between AHI and total cholesterol and an inverse relationship with HDL cholesterol.²⁹ These study differences would further support our hypothesis that sleep characteristics may play a role in the determination of metabolic risk prior to the development or diagnosis of diabetes, and that diabetes masks the effects of perturbed sleep and sleep disorders on cardiovascular risk factors. However, the cross-sectional nature of the present analyses precludes definitive statements.

Some studies have also reported that poor glycemic control, assessed by HbA_{1c}, was associated with low sleep efficiency³⁰ and poor sleep quality,^{30,31} as reported by questionnaire. Actigraphy-measured sleep fragmentation and insomnia, but not sleep duration, was associated with higher fasting glucose, insulin, and HOMA index in patients with type 2 diabetes.³² Similar associations were not observed in those without type 2 diabetes. These studies suggest that poor sleep quality may be related to glycemic control; however, participants were either newly diagnosed with type 2 diabetes (<1 year),³⁰ were at low risk of sleep-related breathing disorders,³¹ or were young adults (approximately 45 years of age).³² These characteristics contrast with the Sleep AHEAD study population, which had longer duration of diabetes, was older, and had a high prevalence of OSA. In addition, sleep variables in the present study were directly measured using PSG.

This study tested the hypotheses that sleep characteristics, including sleep disturbances, would be related to metabolic risk profile in patients with type 2 diabetes. If sleep

disturbances were related to metabolic profile, than it would be expected that treatment of such disturbances would result in an improvement in metabolic risk factors. However, Sharma et al³³ found that continuous positive airway pressure (CPAP) for 3 months improved lipid profile and body composition, with no effect on fasting plasma glucose and insulin in a group of young obese individuals with OSA. These effects were not observed when participants underwent sham CPAP. Of note, however, is that participants had better metabolic risk profiles at the start of sham CPAP than true CPAP, and data were not adjusted for phase order or changes in body composition (although the authors note no phase order effect). Because adipose tissue distribution is strongly associated with metabolic risk factors, it is unknown whether the metabolic improvements with CPAP treatment were due to improvements in OSA or improvements in body composition. On the other hand, withdrawal of CPAP treatment for 2 weeks in individuals who had been undergoing at least 12 months of CPAP treatment did not worsen cholesterol, glucose, or insulin levels and improved triglycerides.³⁴ These results were observed despite a return to OSA within one night of CPAP withdrawal. However, overall, study participants did not have abnormal lipid profiles or glucose metabolism at baseline. It is well known that the effects of CPAP treatment on lipid variables have provided variable results, and readers can refer to a review by Michailidis et al³⁵ for more information on this topic. Such results support the findings of the present study, whereby OSA was not related to any of the metabolic risk factors.

The lack of association between sleep characteristics and lipid variables has been observed by others. In the Nurses' Health Study, sleep duration was not associated with lipid profile in women with type 2 diabetes.³⁶ In the Sleep Heart Health Study,³⁷ total cholesterol did not vary with AHI, although HDL-cholesterol was inversely associated and triglycerides positively associated with AHI in participants < 65 years of age. No association was observed in participants older than 65 years. It is important to note that in the Sleep Heart Health Study, there was a low prevalence of type 2 diabetes, and a small proportion of participants – 16% – had cardiovascular disease at baseline.²⁹ Findings of the SWAN Sleep Study lend some support to the findings of this paper of an association between sleep efficiency and fasting plasma glucose. In the SWAN study, sleep efficiency was inversely related to metabolic syndrome after adjusting for race, menopausal status, health complaints, medication use, smoking, alcohol use, exercise, and BMI.³⁸

The present data are limited by the relative homogeneity of the study population and a relatively small sample size. All participants were overweight or obese, had type 2 diabetes, and 87% had OSA (23% with severe OSA).²² The sample size may have been too small to detect statistically significant associations for some parameters (eg, total cholesterol and AHI, average desaturation/apnea-hypopnea; HDL-cholesterol and sleep duration; triglycerides and percent time in delta sleep) and differences between men and women could not be assessed. Also, independent associations between sleep and metabolic risk factors could have been masked by the stronger effect of obesity³⁹ and also possibly type 2 diabetes. Age may further limit our ability to detect effects of sleep on metabolic risk factors, although age was not related to metabolic risk in the SWAN Sleep Study.³⁸

Sleep data were obtained from a single night of in-home monitoring. Although in-home PSG is well accepted by the sleep community,²³ conditions cannot be controlled. However, participants were tested in their own environment and instructed to go to bed at their usual time, but not given any instruction about specific wake-up time. This in-home testing procedure may have alleviated some of the issues surrounding a single night of PSG measurement, especially as those may arise from sleeping in an unfamiliar environment. Test-retest variability has been found to be lower with in-home PSG compared to in-lab PSG in untreated OSA patients.⁴⁰ Also, although it can be argued that the data used in the present analyses may have been limited by the high night-to-night variability of AHI,⁴⁰ there was no association between other, less variable, sleep measures and metabolic risk factors. However, Quan et al⁴¹ have previously demonstrated no consistent bias in repeated in-home PSG measurements in measures of sleep architecture and quality.

Despite its limitations, the Sleep AHEAD study provided a well-characterized population on whom to study the relationship between sleep parameters and metabolic risk. As a result, it can be concluded that within an overweight and obese group of older patients with established and generally controlled type 2 diabetes, neither sleep disturbances nor duration, assessed by PSG, are strongly associated with metabolic disorders. Sleep characteristics may be more important in individuals without established diabetes or nonobese patients. However, the Sleep AHEAD study is a longitudinal study testing the effects of weight loss on sleep-disordered breathing. Future information from this study may provide additional information concerning the relationship between sleep-disordered breathing and changes in metabolic risk factors over time.

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Disclosure

Dr Sanders is a scientific consultant to Philips-Respironics. Consistent with this he is a coinventor of the BiPAP® brand and related technologies, patents which have been assigned to Philips-Respironics for use with their BiPAP® brand and related technologies and in exchange for a royalty interest. He is an editor-in-chief and section editor (Sleep Medicine section) for the UpToDate website and a field editor for *Sleep Medicine*, and receives remuneration for these activities. He is a deputy editor for *Sleep*. Gary Zammit has received grant funding from Abbott, Actelion, Ancile, Apnex, Arena, Aventis, Cephalon Inc, CHDI, Elan, Epix, Evotec, Forest, Galderma, GlaxoSmithKline, H Lundbeck A/S, King, Merck and Co, Neurim, Neurocrine Biosciences, Neurogen, Organon, Orphan Medical, Otsuka, Pfizer, Predix, Respironics, Sanofi-Aventis, Sanofi-Synthelabo, Schering-Plough, Sepracor, Shire, Somaxon, Takeda Pharmaceuticals North America, Targacept, Thymon, Transcept, UCB Pharma, Predix, Vanda, and Wyeth-Ayerst Research. He is a consultant for Actelion, Alexza, Arena, Aventis, Biovail, Boehringer-Ingelheim, Cephalon Inc, Elan, Eli Lilly, Evotec, Forest, GlaxoSmithKline, Jazz, King Pharmaceuticals, Ligand, McNeil, Merck and Co, Neurocrine Biosciences, Organon, Pfizer, Renovis, Sanofi-Aventis, Select Comfort, Sepracor, Shire, Somnus, Takeda Pharmaceuticals, Vela, and Wyeth. Dr Zammit has also received honoraria from Neurocrine Biosciences, King Pharmaceuticals, McNeil, Sanofi-Aventis, Sanofi-Synthelabo, Sepracor, Takeda Pharmaceuticals, Vela Pharmaceuticals, and Wyeth-Ayerst Research. He is owner/director of Clinilabs Inc, Clinilabs IPA Inc, and Clinilabs Physician Services, PC. Dr Kuna has received grant support from Philips Respironics. All other authors have no conflict of interest to disclose.

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