Differences in Polysomnography Predictors for Hypertension and Impaired Glucose Tolerance

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Rationale: It is unclear which indexes of physiologic stress obtained from polysomnography best predict sleep apnea-related outcomes. We assessed the relationships between various indexes of sleep-associated physiologic stress with 2 outcomes: hypertension and impaired glucose tolerance.

Methods: Three hundred ninety-four participants in the Cleveland Family Study underwent overnight polysomnography, blood pressure measurements, and an oral glucose tolerance test. Graphical techniques and generalized estimating equations for logistic models were used to quantify the relationship between polysomnography indexes and to estimate the odds of each outcome, adjusting for age, sex, race, and body habitus.

Results: Of the sample, 31% had hypertension, and 32% had impaired glucose tolerance. The odds of hypertension increased approximately 20% per 5-unit increase in arousal index (odds ratio 1.22; 95% confidence interval 1.06, 1.41). Weaker associations of hypertension with the apnea-hypopnea index and oxygen-saturation variables were seen. In contrast, the strongest index associated with impaired glucose tolerance was time spent at an oxygen saturation of < 90%; individuals with at least 2% of time spent at a saturation level less than 90% had 2.33 times (95% CI 1.38, 3.94) the odds of impaired glucose tolerance.

Conclusions: These data are consistent with disparate pathways mediating hypertension and impaired glucose tolerance. Vascular responses may be more directly related to sympathetic surges and arousals, whereas metabolic sequelae may be mediated more by hypoxic stress. One single index from polysomnography may not be adequate to fully predict the myriad health outcomes associated with sleep apnea.

Keywords: Sleep apnea, hypertension, diabetes, clinical testing, epidemiology

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INTRODUCTION

OBSTRUCTIVE SLEEP APNEA (OSA), A CONDITION CHARACTERIZED BY INTERMITTENT REDUCTION OF AIRFLOW DURING SLEEP CAUSED BY PHARYNGEAL obstruction, is increasingly recognized as contributing to a substantive public health burden. Healthcare utilization, including hospitalization rates, for individuals with OSA has been estimated to be nearly twice as high as those without OSA.[1,2] This phenomenon likely reflects the common comorbid illnesses that occur with OSA, including hypertension and diabetes.[3-6] These health conditions may occur as a consequence of OSA-related stress, exposing the individual to episodic hypoxemia, sleep fragmentation, and increased sympathetic nervous system activity.

Polysomnography (PSG) has been used to better understand OSA-related comorbidity. In clinic and population-based samples, the apnea-hypopnea index (AHI), measures of hypoxemic stress, and cortical arousals each have been associated with hypertension in analyses that individually or jointly examined such associations.[4,6-10] Insulin resistance and impaired glucose tolerance, conditions recently linked to OSA, also have been found to be associated with various indexes of OSA, including the AHI, with some evidence that indexes of hypoxic stresses explain much of the association with OSA.[3,11]

A further understanding of the health impact of OSA requires the associations of specific OSA-related physiologic stresses to be better defined. Previous research, however, has not consistently applied comprehensive statistical techniques both to define the nature of the exposure-response relationship and to compare the strength of the relationships among a number of related stresses (such as hypoxemia, arousal frequency, and respiratory event frequency) to distinct outcomes. In this analysis, our first aim was to rigorously describe the nature of the relationship (e.g., linear, nonlinear, threshold) between OSA-related physiologic stresses, as derived by PSG, with 2 outcomes: hypertension, and impaired glucose tolerance (IGT). Our second aim was to determine which of the commonly used measures of OSA obtained from PSG, analyzed using the most appropriate exposure-response specification, most consistently predicted each of these 2 health outcomes. For each outcome, we investigated the associations of 5 exposure variables obtained from PSG: the AHI, arousal index, minimum oxygen saturation, average oxygen saturation, and percentage of time with an oxygen saturation of < 90%.

METHODS

Sample

The analytic sample is derived from participants in the Cleveland Family Study, an ongoing genetic epidemiologic cohort study beginning in 1990 and examining the natural history and outcomes of OSA. Recruitment and data-collection methods have been previously described.[12] Briefly, affected families were selected based on the presence of a proband diagnosed with OSA, with neighboring families selected as controls during the first 6 study years. A subsample of 700 of the 2462 cohort members

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This was not an industry supported study. Dr. Redline has served as a scientific advisor for Cypress Bio and Organon. Drs. Sulit, Storfer Isser, and Kirchner have indicated no financial conflicts of interest.

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were targeted for participation in a detailed examination of cardiovascular, sleep, and metabolic traits in an exam occurring between July 2001 and June 2005, based on their potential genetic informativity.[13] At the time of this report, 533 sleep studies had been performed and analyzed. Excluding 4 studies with insufficient sleep time, 14 with alpha intrusion, 60 from subjects using continuous positive airway pressure therapy, and 62 from individuals younger than 16 years of age, resulted in an analytic sample of 394 participants.

Protocol

Participants were studied in a dedicated clinical research facility and underwent overnight 14-channel PSG, blood pressure measurements, venipuncture, anthropometry, and glucose tolerance testing. Prior to the PSG, each participant completed the Cleveland Health and Sleep Questionnaire, a standardized and validated questionnaire assessing sleep habits and symptoms, medical history, health habits, and medication use, including diabetic and antihypertensive medications.[14] Current smokers were identified as answering affirmatively to smoking at least 1 cigarette per day over the prior 1 month; caffeine use was quantified as the number of caffeine-containing drinks consumed on average per day. Height was measured to the nearest centimeter, with the subject in stocking feet, using a wall-mounted stadiometer; weight (to the nearest .1 kg) was measured with a calibrated scale (Healthometer). Body mass index (BMI) was computed as the ratio of weight to the square of the height (kg/m^2). Neck circumference was directly measured using a nonstretchable tape with the subject's head in a Frankford horizontal plane.

Sleep Data Measurements

The PSG data were collected using Compumedics E Series System (Abbotsville, Victoria, Australia). The recording montage consisted of C_3/A_2 and C_4/A_1 electroencephalograms, right and left electrooculograms, a bipolar submental electromyogram, thoracic and abdominal respiratory inductance plethysmography, "airflow" (by nasal-oral thermocouple), nasal pressure (via a nasal cannula), oximetry (Nonin Medical, Inc., Plymouth, MN), electrocardiogram, body position (by a mercury gauge sensor), and bilateral leg movements (by piezo sensors). Each study was scored by 1 certified research technologist.[15] Sleep staging and arousals were scored using Rechtschaffen and Kales criteria[16] and recommended criteria from the American Sleep Disorders Association,[17] respectively. Apneas and hypopneas were defined using Sleep Heart Health Study criteria modified to include nasal pressure.[18] An apnea was defined as a complete or almost complete reduction in the thermocouple signal, lasting longer than 10 seconds. Hypopneas were scored when the amplitude of the sum of the abdominal and thoracic inductance signals or the nasal pressure flow signal were clearly reduced for longer than 10 seconds, with reductions at least 30% below "baseline" breathing amplitude. Each respiratory event was linked to data from the oxygen saturation and electroencephalogram channels (arousals). We used a hypopnea definition that required a minimum of a 3% desaturation to be observed with each event. The arousal index was defined as the number of arousals per hour of sleep. Intrarater reliability for the arousal index for the scorer who analyzed all studies was formally assessed in a scoring-reliability assessment, showing an intraclass correlation coefficient of 0.96.

Blood Pressure Measurement

Participants had 3 supine blood pressure measurements, each performed after lying quietly for 10 minutes, before bed (10:00 PM) and upon awakening (7:00 AM), and another 3 sitting at 11:00 AM, following standardized guidelines using a calibrated sphygmomanometer.[19] Cuff size was determined by the circumference of the upper arm and the appropriate bladder size from a standard chart. Blood pressure was determined as the average of the 9 measurements.

Glucose Tolerance Measurement

Both fasting blood glucose and oral glucose tolerance (in nondiabetics) were assessed in the morning following the PSG. Fasting blood glucose was measured by venipuncture upon awakening (7:00 AM). This was followed by assessment of glucose tolerance testing, in which 75 grams of anhydrous glucose was orally administered, with venipuncture performed 2 hours later for glucose and insulin levels.

Outcomes

We examined 2 sleep apnea-associated outcomes: hypertension and IGT. Participants were considered to have hypertension either (1) if their average systolic or diastolic blood pressure was $\geq$ 140 mm Hg or $\geq$ 90 mm Hg, respectively or (2) if they answered affirmatively to use of antihypertensive medications in the past year.

Participants were considered to have IGT if (1) their fasting glucose was glucose $\geq$ 110 mg/dL, or if (2) their serum glucose 2 hours post glucose load was $\geq$ 140 mg/dL, or (3) if they answered affirmatively to using diabetic medications in the past year.

Statistical Analysis

Subject characteristics and sleep indexes are summarized using means, standard deviations, and medians for continuous variables and frequencies and proportions for categorical variables. To investigate the exposure-response relationship of each predictor with each outcome, scatterplots and restricted cubic splines were utilized.[20] Restricted cubic splines relax the strict assumption of linearity that is often assumed for a continuous predictor by the model to more closely approximate the true relationship. These results were used to select the functional form of each predictor for the main analyses. Results suggesting a linear relationship with the outcome were included as continuous predictors, whereas results suggesting a threshold relationship were dichotomized at a clinically meaningful cutoff consistent with the threshold value. Generalized estimating equations with an exchangeable within-family correlation structure and robust variance estimate were used to estimate the odds of each outcome without covariate adjustment, as well as adjusting for age, African-American race, sex, BMI, neck circumference, smoking status, and caffeine use. Results are summarized using odds ratios (OR) and 95% confidence intervals (CI). All analyses were performed using SAS version 9.1.3 (SAS Institute Inc, Cary, NC).

Table 1—Characteristics of the Total Sample and by Hypertension and Impaired Glucose Tolerance

Characteristic	Analytic Sample (n = 394)[a]	Neither IGT nor hypertension (n = 210)	IGT Only (n = 59)	Hypertension Only (n = 54)	Both IGT & hypertension (n = 67)
Age, y	43.2 ± 17.0 (44.6)	35.7 ± 14.9 (33.2)	47.2 ± 17.3 (47.7)	50.7 ± 11.7 (50.4)	57.9 ± 12.4 (55.9)
Male	177 (44.9%)	82 (39.1%)	39 (66.1%)	18 (33.3%)	35 (52.2%)
African American	187 (47.5%)	94 (44.8%)	22 (37.3%)	30 (55.6%)	38 (56.7%)
BMI, kg/m^2	32.3 ± 8.2 (30.8)	30.0 ± 7.6 (28.9)	34.4 ± 7.4 (33.7)	34.9 ± 8.3 (33.9)	36.0 ± 8.3 (34.0)
Obese[b]	221 (56.1%)	91 (43.3%)	44 (74.6%)	36 (66.7%)	50 (74.6%)
AHI, events/h	14.5 ± 20.9 (5.5)	8.4 ± 14.3 (2.4)	18.1 ± 21.3 (12.0)	17.4 ± 22.9 (10.2)	28.7 ± 28.1 (18.5)
AHI Category					
0 to < 5	188 (47.7%)	131 (62.4%)	20 (33.9%)	20 (37.0%)	13 (19.4%)
5 to < 15	90 (22.8%)	44 (21.0%)	16 (27.1%)	15 (27.8%)	15 (22.4%)
15 to <30	60 (15.2%)	21 (10.0%)	12 (20.3%)	12 (22.2%)	15 (22.4%)
30+	56 (14.2%)	14 (6.7%)	11 (18.6%)	7 (13.0%)	24 (35.8%)
Arousal index, events/h	15.8 ± 10.0 (13.7)	13.6 ± 7.4 (12.0)	15.3 ± 8.0 (14.2)	18.5 ± 13.4 (15.4)	21.2 ± 13.2 (16.2)
Percentage of time with O_2 sat < 90%	4.0 ± 11.7 (0.1)	1.2 ± 4.8 (0.0)	6.3 ± 13.1 (1.0)	4.0 ± 9.8 (0.4)	11.0 ± 20.8 (2.1)
Min O_2 sat	85.3 ± 7.6 (87.0)	87.6 ± 6.2 (89.5)	83.8 ± 7.2 (86.0)	84.2 ± 6.8 (85.5)	80.9 ± 8.9 (83.0)
Average O_2 sat	94.9 ± 2.3 (95.1)	95.7 ± 1.6 (96.0)	94.0 ± 2.2 (94.1)	94.4 ± 2.0 (94.8)	93.3 ± 3.1 (94.0)

Data are presented as mean ± SD and median for continuous variables and number and percentage for categorical variables. AHI refers to apnea-hypopnea index; O_2 sat, oxygen saturation.
[a]Includes 4 participants without hypertension and with unknown impaired glucose tolerance (IGT)
[b]Obesity is defined as a body mass index (BMI) > 30.

Table 2—Spearman Correlations among Polysomnographic Indexes*

	AHI	Arousal Index	Percentage of time with O_2 sat < 90%	Average O_2 sat	Min O_2 sat
AHI	1.00		Min O_2 sat		
Arousal Index	0.51	1.00	Average O_2 sat		
Percentage of time with O_2 sat < 90%	0.78	0.33	1.00		
Average O_2 sat	-0.64	-0.30	-0.75	1.00	
Min O_2 sat	-0.72	-0.24	-0.87	0.66	1.00

*All correlations significant at p<0.001.
AHI refers to apnea-hypopnea index; O_2 sat, oxygen saturation.

RESULTS

Sample Characteristics

Characteristics of the analytic sample are shown in Table 1. The sample had an average age of 43 years, 45% were male, and 48% were African American. The sample included 221 subjects (56%) who were obese (BMI ≥ 30). A wide range of OSA was observed, with 52% with an AHI ≥ 5, and median levels of AHI and arousal index of 5.5 and 13.7, respectively. Approximately 31% of participants (n = 121) had hypertension, and 32% (n=126) had IGT. Sixty-seven (17%) of participants were classified with both hypertension and IGT.

Sample Characteristics by Hypertension and IGT

Sample characteristics stratified by hypertension and IGT status are presented in Table 1. Compared with those with neither hypertension nor IGT, participants with hypertension were significantly older, heavier, and more likely to be African American (all p values < .05). Approximately half of subjects with hypertension (55%) also had IGT. Hypertensive participants had significantly greater levels of sleep disturbance on all 5 PSG measures. Those with hypertension had a significantly higher AHI (23.6 vs 10.4), arousal index (20.0 vs 13.9), and percentage of time with an oxygen saturation < 90% (7.9% vs 2.3%) and significantly lower average sleep oxygen-saturation level (93.8% vs 95.4%) and minimum oxygen saturation (82.4% vs 86.7%) than participants without hypertension (all p values < .01).

Compared with participants without IGT, those with IGT (with or without hypertension) also were significantly more likely to be older (52.9 vs 38.7 years), heavier (BMI 35.2 vs 31.0 kg/m^2), and male (58.7% vs 37.9%) (all p values < .0001). Those with IGT were also significantly more likely to be hypertensive (53.2% vs 20.5%, p < .0001). Similar to the hypertension group, participants with IGT had significantly greater levels of sleep disturbance, compared with those without IGT. Participants with IGT had significantly higher levels of AHI (23.7 vs 10.2), arousal index (18.4 vs 14.6), and percentage of time with an oxygen saturation < 90% (8.8% vs. 1.8%) and significantly lower average oxygen saturation (93.6% vs 95.5%), and minimum oxygen saturation (82.3% vs 86.9%) (all p values < .001).

Participants with both hypertension and IGT tended to be older and heavier and to have more severe levels of sleep-disordered breathing than did individuals with either hypertension or IGT (Table 2).

Interrelationships Among PSG Indexes

Table 2 shows the Spearman correlation coefficients relating the strength of the linear associations among the 5 PSG indexes studied. As expected, the various measures of nocturnal desaturation were highly correlated. The AHI and arousal index were also strongly correlated. However, the arousal index and indexes of nocturnal desaturation were only modestly correlated (r: 0.24 to 0.33).

Table 3—Unadjusted and Adjusted Generalized Estimating Equations Modeling the Odds of Hypertension

	Unadjusted	p Value	Adjusted[a]	p Value
AHI[b]	1.33 (1.15, 1.53)	< .0001	1.14 (0.99, 1.32)	.0711
Arousal index[c]	1.33 (1.18, 1.49)	< .0001	1.22 (1.06, 1.41)	.0069
≥ 2% time < 90% saturation	3.36 (1.90, 5.96)	< .0001	1.19 (0.56, 2.50)	.6558
< 95% average saturation	4.09 (2.64, 6.33)	< .0001	1.69 (0.86, 3.31)	.1289
< 90% minimum saturation	5.06 (2.91, 8.80)	< .0001	1.59 (0.79, 3.21)	.1927

[a]Models adjusted for age, male, African-American, body mass index, neck circumference, current smoking status, and average daily caffeine consumption.
[b]Apnea-hypopnea index (AHI) odds ratio shown for a 10-unit (0.5-SD) change.
[c]Arousal index odds ratio shown for a 5-unit (0.5-SD) change.

Table 4—Unadjusted and Adjusted Generalized Estimating Equations Modeling the Odds of Impaired Glucose Tolerance

	Unadjusted	p Value	Adjusted*	p Value
AHI[†]	1.34 (1.18, 1.53)	< .0001	1.04 (0.91, 1.18)	.5816
Arousal index[††]	1.18 (1.04, 1.33)	.0095	0.96 (0.83, 1.09)	.5040
≥ 2% time < 90% saturation	6.03 (3.51, 10.37)	< .0001	2.33 (1.38, 3.94)	.0015
< 95% average saturation	3.83 (2.49, 5.88)	< .0001	1.30 (0.79, 2.16)	.3071
< 90% minimum saturation	3.19 (1.84, 5.54)	< .0001	0.85 (0.42, 1.71)	.6397

*Models adjusted for age, male, African-American, body mass index, neck circumference, current smoking status, and average daily caffeine consumption.
[†]Apnea-hypopnea index (AHI) odds ratio shown for a 10-unit (0.5-SD) change.
[††]Arousal index odds ratio shown for a 5-unit (0.5-SD) change

Exposure-Response Relationships for Sleep Variables and Hypertension and IGT Outcomes

For both hypertension and IGT outcomes, unadjusted and adjusted graphical analyses, using restricted cubic splines, indicated that the arousal index and AHI had an approximately linear exposure-response relationship, whereas the oxygen-saturation variables had a threshold effect (with a dichotomy showing a better fit to the relationship than a linear term). The threshold values for the oxygen-saturation variables that best approximate observed increases in the odds of each outcome were 2% for percentage of time spent with an oxygen saturation < 90%, 95% for average oxygen saturation, and 90% for minimum oxygen saturation. The oxygen-saturation measures were then fitted as dichotomous predictors, whereas arousal index and AHI were retained as continuous variables.

Generalized estimating equations models without covariate adjustment, as well as adjusting for age, sex, race, BMI, neck circumference, smoking status, and caffeine use were fitted to predict the odds of hypertension (Table 3) and IGT (Table 4). The odds ratio represents a 10-unit change for AHI and a 5-unit change for arousal index, which was approximately a 0.5-SD change for each predictor. The results show that whereas all of the predictors are significantly associated with hypertension in unadjusted analyses, only arousal index was a significant predictor in adjusted analyses. The odds of hypertension increased by approximately 22% with each 5-unit increase in the number of arousals per hour, controlling for age, sex, race, BMI, neck circumference, smoking status, and caffeine use (OR = 1.22, 95% CI: 1.06, 1.41, p = .007). AHI had a marginally significant association with hypertension; for each 10-unit increase in AHI, the odds of hypertension increased by 14% (OR = 1.14, 95% CI: 0.99, 1.32, p = .070).

Similar to the hypertension results, all of the predictors had a statistically significant association with IGT in unadjusted analyses. However, only percentage of sleep time spent with an oxygen saturation less than 90%—dichotomized at 2%—was a significant predictor of IGT after covariate adjustment. The results showed that after controlling for age, sex, race, BMI, neck circumference, smoking status, and caffeine use, participants with at least 2% of their sleep time at less than 90% oxygen saturation had more than twice the odds of IGT compared with those with less than 2% of sleep time at less than 90% oxygen saturation (OR = 2.33; 95% CI: 1.38, 3.94, p = .002).

To better understand the relationship between the arousal index and hypertension, the arousal index was divided into 2 components: arousals associated with a respiratory event and arousals not associated with a respiratory event. Secondary analyses included each of these measures as predictors of hypertension, and generalized estimating equations models were fitted with and without covariate adjustment. These results showed that arousals occurring independently of a respiratory event were not a significant predictor of hypertension in unadjusted and adjusted analyses. However, arousals associated with respiratory events were a statistically significant predictor of hypertension in both unadjusted and adjusted analyses. After covariate adjustment, each 5-unit increase in the number of arousals associated with a respiratory event per hour was associated with an 18% increase in the odds of hypertension (OR = 1.18, 95% CI: 1.03, 1.36, p = .018).

For models predicting both hypertension and IGT, we additionally tested for interactions between the arousal index and measures of desaturation, none of which was statistically significant.

DISCUSSION

A growing body of research demonstrates that OSA is associated with several cardiovascular and metabolic outcomes. In particular, 2 common chronic health conditions—hypertension and impaired glucose tolerance or diabetes—have been shown to be associated with OSA, as measured using several indexes of apnea frequency or oxygen desaturation.[6,11,21-27] Each outcome, however, may be related to OSA through distinct pathophysiologic pathways that differentially reflect responses to hypoxemia, arousal, and sleep deprivation and to other physiologic perturbations. We are unaware of existing literature that has reported parallel analyses of the relationships of various PSG indexes of physiologic

stress to OSA outcomes, hypertension, and IGT. Additionally, most prior analyses have assumed either a linear "exposure-response" relationship or a single threshold response based on a clinical threshold definition of OSA, without rigorous assessment of the validity of such assumptions.

This series of analyses yielded 2 major findings. First, in adjusted analyses, we observed marked differences in which indexes of physiologic stresses best predicted each of the examined OSA-related outcomes. The arousal index was the strongest predictor for hypertension, whereas measures of oxygen desaturation provided the strongest predictors of IGT. Second, a rigorous evaluation of the associations of 5 PSG measures with each outcome demonstrated unique exposure-response relationships. A linear relationship was observed between the AHI and the arousal index with hypertension. In contrast, a threshold dose response was demonstrated with the measures of hypoxic stress and IGT.

Epidemiologic studies have demonstrated that OSA and hypertension are linked.[4,6,27] This relationship likely is mediated by intermittent hypoxia, flow limitation, and sleep fragmentation, possibly acting synergistically, to augment sympathetic activity.[28-34] In humans, a role for increased sympathetic activity in OSA-related hypertension is suggested by studies showing elevations in urinary catecholamine excretion and enhanced vascular reactivity in individuals with OSA compared with controls.[7,30,35-37] Furthermore, effective treatment of OSA patients with continuous positive airway pressure has been shown to reduce peroneal muscle sympathetic activity, a measure of sympathetic tone.[38] Experimental studies suggest that sympathetic nervous system activity and hypertensive responses are greatest after exposures to combinations of arousal, hypoxemia, and airway obstruction. For example, a canine model has demonstrated that apnea-induced arousals result in neurally mediated blood pressure increases, with larger blood pressure elevations observed in the presence of cortical arousals than when apneas are terminated prior to the occurrence of arousal.[39] Nonrespiratory arousals, as induced by auditory stimuli, in contrast, may result in acute blood pressure elevations but not in sustained daytime hypertension.[28] In addition, experimentally induced hypoxemia occurring without airway obstruction is a much less potent blood pressure stimulus than is hypoxemia occurring with apnea.[40] Our data are consistent with this prior work, showing that, among commonly derived PSG indexes, the arousal index was the PSG measure that was most strongly associated with hypertension, with secondary analyses suggesting that it was only respiratory-related arousals that were associated with hypertension. Additionally, we did not demonstrate significant associations between several measures of overnight hypoxemia and hypertension, further indicating the relevance of measures that capture hypoxemia occurring in combination with airflow obstruction or arousal, as predictors of hypertension.

Our finding that the arousal index best predicts hypertension in a predominantly middle-aged population is consistent with data from the Wisconsin Cohort Study, showing that sleep fragmentation is associated with an increased in blood pressure in individuals with an AHI of less than 1,[41] and other studies that have shown that snoring, sometimes in a setting of a low AHI but with sleep fragmentation,[42,43] is associated with hypertension. Other human studies also suggest that overnight blood pressure changes are closely related to measures of respiratory effort.[44] In aggregate, these data support a central role for respiratory-related sleep fragmentation in hypertensive disease.

Previous epidemiologic research generally has shown inconsistent findings related to PSG predictors of hypertension. In the Sleep Heart Health Study, an AHI of 30 or greater was associated with an odds of 1.37 for hypertension; the arousal index was associated with a slightly lower and not statistically significant increased odds.[6] The lower effects estimated for arousal index in that study may have been related to the lower scoring reliability of this index, compared with the AHI,[5] or to examination of a predominantly older population, in whom autonomic nervous system and arousal responses may be less robust than those in younger samples.[46] The emergence of the arousal index as the strongest PSG predictor in the current study may reflect examination of a younger population, in whom studies with alpha intrusion (which may reduce scoring reliability) were excluded, and use of studies that were scored by a single scorer with documented high intrascorer reliability.

It should be noted that measurement of cortical arousals during PSG requires collection of data from electroencephalography and electromyography and scoring of such data by highly trained scorers. Although arousal scoring is labor intensive, collection of such data has been advocated as a means for providing indirect information on sympathetic nervous system activation. The putative utility of this is suggested by electrophysiologic studies in mice that have shown strong correlations between the firing of adrenergic neurons and arousal state. Smaller human studies[34,47] have shown that movement arousals may influence sympathetic tone and abnormal circadian rhythm of blood pressure. However, newer techniques, such as peripheral arterial tonometry,[48] or pulse transit time[49] may provide even more specific measures of sympathetic nervous system activation than that obtained from cortical electroencephalogram changes and may be particularly useful to predict OSA-related hypertension.

More recently, the relationship between OSA and IGT or diabetes has emerged as an area of great interest. Early studies demonstrated higher levels of insulin resistance—defined as abnormal fasting glucose, insulin, or glucose tolerance testing—in groups of snorers or apneics, compared with controls.[5,50] Animal studies seeking to define mechanistic pathways have suggested that increased insulin resistance may result from specific hypoxic stresses.[51-53] Limited human data have attempted to dissect the associations of overnight hypoxemia from other OSA stresses. However, using different measures of OSA severity, Punjabi et al demonstrated in 2 human samples that hypoxic stress was the best predictor of glucose intolerance and insulin resistance after controlling for BMI, age, sex, and race.[3,11] Underlying mechanisms that mediate hypoxia and diabetes may be linked to several factors, including regulation of leptin, a hormone that can alter insulin levels and resistance.[53-55] In addition, hypoxia may also lead to subsequent generation of reactive oxygen species and other various inflammatory cytokines,[56] which may also contribute to altered glucose metabolism.

The strengths of this study include assessment of associations in a diverse sample with a wide range of AHI and use of standardized PSG with scoring performed by a single certified scorer to maximize reliability. In addition, the availability of both oral glucose tolerance testing and fasting glucose and insulin levels and multiple measures of blood pressure allowed rigorous assessment of all outcomes. The potential limitations of this study include the use of a data from a family cohort with inclusion of some individuals at increased genetic risk for OSA. However, all analyses

were adjusted for within-familial clustering; the high estimated inheritance of the disorder[13] suggests that data from such a cohort are likely to be generalizable to other samples. However, since the sample size was only moderately large, subgroup analyses were not feasible, and there was more limited power to detect small to modest effects. Another limitation is that all analyses were cross-sectional, limiting causal inferences. Future analyses of prospectively collected data are required to further define causal associations.

In summary, parallel analyses of several exposures and 2 OSA outcomes identified differences in the exposure-response relationships for varying predictor-outcome associations and differences in the strength of different PSG predictors to each health outcome. The linear monotonic response of the arousal index and AHI with hypertension and the threshold response for oxygen saturation with IGT raise interesting points of consideration. First, in studying the associations between PSG measures and OSA-related morbidity, caution should be used when assuming specific exposure-response relationships, and common clinical "cutoffs" for threshold values may or may not describe the appropriate functional form of the covariate. Furthermore, although current clinical practice uses a threshold number of apneas and hypopneas to define the presence of OSA, our results suggest that there is no threshold response between level of the arousal index or AHI with hypertension. Second, the disparate associations for hypertension and IGT suggest that different pathophysiologic pathways may mediate OSA-related outcomes. It is plausible that OSA and hypertension are more strongly linked through sympathetic overactivity and surges in catecholamines or vascular reactivity mediated by repetitive arousals. In contrast, OSA-related IGT is more likely mediated by pathways that are influenced by hypoxia but may not directly involve arousals. Our findings suggest caution in recommending any specific measurement as "optimal" in characterizing OSA-related stress. Our data, rather, suggest that the multiple parameters obtained by PSG may differentially predict different outcomes, and any 1 measure may not be optimal for predicting the wide range of comorbidity observed with OSA.

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