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Sleep-Disordered Breathing and Impaired Glucose Metabolism in Normal-Weight and Overweight/Obese Individuals

The Sleep Heart Health Study

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OBJECTIVE— To characterize the association between sleep-disordered breathing (SDB) and impaired fasting glucose (IFG), impaired glucose tolerance (IGT), combined IFG and IGT, and occult diabetes in individuals of different body habitus.

RESEARCH DESIGN AND METHODS— Cross-sectional analysis of 2,588 participants (aged 52–96 years; 46% men) without known diabetes. SDB was defined as respiratory disturbance index ≥ 10 events/h. IFG, IGT, occult diabetes, and body weight were classified according to recent accepted guidelines. Participants with and without SDB were compared on prevalence and odds ratios for measures of impaired glucose metabolism (IGM), adjusting for age, sex, race, BMI, and waist circumference.

RESULTS— SDB was observed in 209 nonoverweight and 1,036 overweight/obese participants. SDB groups had significantly higher adjusted prevalence and adjusted odds of IFG, IFG plus IGT, and occult diabetes. The adjusted odds ratio for all subjects was 1.3 (95% CI 1.1–1.6) for IFG, 1.2 (1.0–1.4) for IGT, 1.4 (1.1–2.7) for IFG plus IGT, and 1.7 (1.1–2.7) for occult diabetes.

CONCLUSIONS— SDB was associated with occult diabetes, IFG, and IFG plus IGT, after adjusting for age, sex, race, BMI, and waist circumference. The magnitude of these associations was similar in nonoverweight and overweight participants. The consistency of associations across all measures of IGM and body habitus groups and the significant association between SDB and IFG plus IGT, a risk factor for rapid progression to diabetes, cardiovascular disease, and mortality, suggests the importance of SDB as a risk factor for clinically important levels of metabolic dysfunction.

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Abbreviations: FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGM, impaired glucose metabolism; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; RDI, respiratory disturbance index; SDB, sleep-disordered breathing; SHHS, Sleep Heart Health Study.

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Sleep-disordered breathing (SDB) is a chronic illness characterized by repetitive episodes of partial or complete cessation of breathing during sleep, which may affect up to 17% of middle-aged adults (1) and 20% of older adults in the U.S. (2). Chronic sleep fragmentation, sleep deprivation, and intermittent nocturnal hypoxemia associated with SDB have been implicated in metabolic dysfunction, including altered glucose metabolism (3,4). Increasing evidence suggests a link between SDB and type 2 diabetes, glucose intolerance, and insulin resistance (5–10). Difficulties in interpreting previous studies, however, relate to concerns over the adequacy by which overweight, a potential confounder associated both with SDB and disorders of glucose (11), was addressed. Furthermore, prior work has not specifically addressed whether distinct indicators of pre-diabetes (impaired fasting glucose [IFG], impaired glucose tolerance [IGT], or both) are differentially associated with SDB. IFG, introduced in 1997 by the American Diabetes Association as an analog to IGT, has been shown to identify a subgroup of the population with possibly different pathophysiology, subclinical characteristics, and risks of conversion to diabetes and comorbidities (12–14). Increasing research shows only a moderate level of concordance between classification of pre-diabetes states based on IFG and IGT. Specifically, only 45% of subjects who demonstrate IFG also have IGT, and, conversely, 25% or less of those found with IGT also have IFG (13,15–18). Glucose dysregulation with combined IFG plus IGT is considered to represent an advanced stage of pre-diabetes and, compared with isolated IGT or isolated IFG, has a distinctly higher risk of conversion to diabetes and more severe associated comorbid illnesses (12,19–21). Intermediate states (IFG, IGT, and IFG plus IGT) of transition to diabetes have generated increasing pathophysiological and clinical interest in an effort to prevent or delay the

onset of diabetes and associated cardiovascular disease (19–22).

The purpose of this study was to characterize the association between SDB and each available index of impaired glucose metabolism (IGM) (IFG, IGT, combined IFG plus IGT, and undiagnosed diabetes). Adjusted prevalence for each of these different states of glucose dysregulation was calculated, and the consistency of the relationships was analyzed across weight categories. We examined data from a large, community-based study to address the hypothesis that individuals with a BMI <25 kg/m² and SDB have a higher adjusted prevalence and odds of IFG, IGT, IFG plus IGT, and occult diabetes compared with individuals from the same BMI group who do not have SDB. Similar trends are expected within the overweight/obese group (BMI ≥25 kg/m²). We also explored the hypothesis that individuals with SDB are at increased odds for IFG plus IGT, a marker for risk of rapid progression to diabetes, recurrence of episodes of myocardial ischemia (12), and premature death (13,14).

RESEARCH DESIGN AND METHODS

Analyses were based on a subset of data obtained from community-dwelling participants of the Sleep Heart Health Study (SHHS). The SHHS is a large multicenter cohort study designed to examine the association between SDB and cardiovascular disease. Between 1994 and 1999, 6,441 participants underwent home polysomnography and completed a set of questionnaires on general health and sleep habits. Detailed study aims and design are described elsewhere (23). Informed consent was obtained from all participants after the institutional review boards of each participating institution approved the study protocol. The analysis sample consisted of a subset of 2,588 individuals with data for both fasting plasma glucose (FPG) and 2-h postload glucose levels from a 75-g oral glucose tolerance test (OGTT) and who were not receiving oral hypoglycemic or insulin therapy. These participants were members of two SHHS parent studies that collected glucose data in close proximity to the SHHS: the Cardiovascular Health Study (*n* = 900) and the Atherosclerosis Risk in Communities Study (*n* = 1,688). Detailed study aims and designs of these parent studies have been described elsewhere (24,25). Blood sampling was before the polysomnogram: in 75% of cases this occurred within a 12-

month interval and in 96.5% within an 18-month interval.

Polysomnography

Unattended overnight polysomnography was performed using the Compumedics Portable PS-2 System (Compumedics Sleep, Abbotsville, Australia). Details on physiological parameters recorded, type of equipment used, monitoring and scoring procedures, and quality assurance are described in detail elsewhere (26). Sleep stages were assigned according to published guidelines (27,28). The respiratory disturbance index (RDI) was calculated as the number of apneas and hypopneas (each associated with a ≥3% decrease in oxyhemoglobin saturation) per hour of sleep (29). SDB was defined as RDI ≥10 respiratory events per hour. This was determined based on preliminary analyses, using restricted cubic splines, which suggested an RDI threshold in the neighborhood of 10 on both FPG and IGT. Sensitivity analyses were performed using alternative definitions for SDB, with RDI thresholds at ≥5, ≥12, and ≥15 respiratory events per hour.

Metabolic assessments

Venous blood was sampled after an overnight fast of at least 12 h and also 2 h after a 75-g dose of glucose was orally administered. The serum was stored at -70°C, and serum glucose levels were measured using the hexokinase method. Based on the most recent recommendations (15), IFG was defined when FPG ≥100 mg/dl and <126 mg/dl and IGT was defined when OGTT ≥140 mg/dl and <200 mg/dl. Subjects were classified with occult diabetes by two different classification strategies: 1) FPG ≥126 mg/dl and 2) OGTT 2-h post challenge glucose ≥200 mg/dl. Sensitivity analyses were also performed using the older definition for IFG (where FPG ≥110 mg/dl and FPG <126 mg/dl) (16).

Anthropometry

Weight was measured using a calibrated portable scale on the night of the polysomnography while the subject wore light clothes. Height was directly measured during a study visit conducted as part of the parent study exam. BMI was calculated as weight in kilograms divided by the square of the height in meters (kg/m²). For stratified analyses, overweight was defined according to the National Institutes of Health clinical guidelines for adults as a BMI ≥25 kg/m² (30). Waist

circumference was also measured on the night of the polysomnography, using a nonstretchable tape around the minimal area over the umbilicus. Covariates of interest included age (years), sex, and race (white/nonwhite, according to self-report).

Statistical analysis

Descriptive statistics including median, interquartile range, and frequencies for continuous and categorical data are presented for all participants and by the SDB and weight categories. The Wilcoxon rank-sum and Pearson's χ^2 tests were used to compare subject characteristics between SDB and non-SDB individuals within each weight group. Logistic regression analysis was used to model the association of each binary outcome variable (IFG, IGT, IFG plus IGT, and occult diabetes) with SDB, the primary exposure variable, adjusted for age, sex, race, BMI, and waist circumference (30–32). All models were assessed for multicollinearity using the variance inflation factor. Sensitivity analyses were conducted to further extend the interpretation, using different cutoff points for BMI (27,30) and IFG (100 mg/dl and 110 mg/dl), as well as to examine the consistency of associations between each parent cohort (Atherosclerosis Risk in Communities Study and Cardiovascular Health Study). All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

Sample characteristics

The analytic sample had slightly more women (54%) and was primarily white (94%), with a median age of 67 years (Table 1). Mean BMI was 28.2 kg/m², with 74% of participants classified as overweight or obese (BMI ≥ 25 kg/m²), including 30% classified as obese (BMI ≥ 30 kg/m²). A wide range of RDI values was observed, with median RDI levels in the mild to moderate range (9–20 events/h), and 48% of participants were classified as having SDB based on a threshold RDI of 10. Among those individuals with SDB, 83% were overweight or obese and 41% were obese.

Table 1 also summarizes the distribution of other subject characteristics, including indexes of glucose dysregulation and RDI, for each group across SDB and weight categories. Subjects with SDB in both weight categories included a higher percentage of men and older individuals. Even within each weight category, the

Table 1—Subject characteristics in the analytic sample and according to weight and SDB* status

	Total participants	Nonoverweight (n = 679)*			Overweight/obese (n = 1,909)†		
		No SDB	SDB	P value	No SDB	SDB	P value
n	2,588	470	209		873	1,036	
Age	67 (60–75)	66 (59–75)	75 (67–80)	<0.0001	66 (59–74)	68 (61–74)	0.001
Men	1,196 (46.2)	136 (28.9)	107 (51.2)	<0.0001	320 (36.7)	633 (61.1)	<0.0001
White race	2,428 (93.8)	449 (95.5)	196 (93.8)	0.330	813 (93.1)	970 (93.6)	0.70
FPG test (mg/dl)	96 (90–104)	93 (87–98)	92 (87–101)	0.390	96 (91–103)	100 (93–108)	<0.0001
OGTT (mg/dl)	128 (102–162)	116 (94–148)	119 (96–157)	0.140	128 (101–162)	136 (108–170)	0.0002
RDI‡	9.4 (4–19)	3 (1–6)	18 (13–26)	<0.0001	5 (3–7)	20 (14–32)	<0.0001
BMI (kg/m ²)	27.6 (24.9–30.7)	23 (21.8–24.2)	23.3 (22–24)	0.240	28.3 (27–31)	29.9 (28–33)	<0.0001
Waist circumference (cm)	98 (91–106)	86 (80–92)	89 (82–93)	0.008	100 (94–106)	104 (98–112)	<0.0001

Data are median (interquartile range) for continuous variables or n (%), unless otherwise indicated. *BMI <25 kg/m². †BMI ≥25 kg/m². ‡RDI: respiratory events per hours each associated with ≥3% decreases in oxyhemoglobin saturation.

subgroups with SDB were more likely to be men, likely to be older, and had higher levels of BMI and waist circumferences than their counterparts without SDB. In the overweight group, fasting and post-glucose load glucose levels were significantly higher in those with SDB compared with those without SDB.

Significantly higher adjusted prevalence rates of IFG, IFG plus IGT, and occult diabetes were found in the SDB group when compared with the non-SDB group for the entire sample (Table 2). Within the overweight group, over one in three SDB participants were found with IFG or IGT, one in six with both IFG and IGT, and up to one in eight with occult diabetes; the prevalence of each index of IGM was higher in the SDB subgroup compared with the subgroup without SDB. In the nonoverweight SDB group, approximately one-fourth had IFG, one-third had IGT, and one-tenth was found positive for both IFG and IGT, after controlling for age, sex, race, BMI, and waist circumference. Similar to the overweight group, the adjusted prevalence rates for all indexes of IGM were higher in the SDB compared

with the non-SDB group, with group differences statistically significant for IFG, IFG plus IGT, and occult diabetes (OGTT >200 mg/dl).

Table 3 shows the results of univariate and multiple logistic regressions analysis for each measure of glucose dysregulation. In the entire analytic sample, the SDB group had significantly increased unadjusted odds of IGM, compared with the non-SDB group, for each index of IGM. With adjustment for covariates, odds ratios were modestly attenuated but remained significant for each index other than for IGT, with point estimates that were highest for occult diabetes defined on the basis of fasting glucose. In analyses stratified by BMI level, similar patterns were observed, with relatively higher point estimates observed for occult diabetes. For each index of IGM, somewhat higher adjusted point estimates were observed for SDB among the nonoverweight group than the overweight/obese group, although due to the much smaller sample size, the CIs were broader. Similar findings were obtained when running sensitivity analyses using alternative

thresholds for IFG (110 mg/dl), SDB (RDI cutoff of 5, 12, and 15 events/h), new BMI categories by obese status (BMI cutoff of 30 kg/m²), and for each parent cohort analyzed separately. Other analyses, using data from the both weight groups, evaluated models that included an interaction term between weight category and SDB status. In no model was this interaction significant, which is consistent with similarities of SDB associations across weight strata.

CONCLUSIONS— These analyses extend previous findings between SDB and glucose metabolism (3,5–10) by rigorous assessment of potential confounding by overweight/obesity and by exploring whether distinct indexes of IGM (IFG, IGT, and IFG plus IGT) are differentially associated with SDB in both normal-weight (BMI <25 kg/m²) and overweight/obese subgroups. The findings strengthen the evidence for an independent association between SDB and IGM, which is not explained by BMI or waist circumference. Although the limited number of nonoverweight/obese par-

Table 2—Adjusted prevalence of IGM in all participants and according to weight and SDB status*

IGM*	Total participants (n = 2,588)			Nonoverweight (n = 679)†			Overweight/obese (n = 1,909)‡		
	No SDB	SDB	P value	No SDB	SDB	P value	No SDB	SDB	P value
n	1,343	1,245		470	209		873	1,036	
IFG	30.8	37.4	0.002	17.6	25.5	0.03	36.9	43.0	0.02
IGT	31.4	34.9	0.11	24.6	31.5	0.09	34.0	36.5	0.33
IFG plus IGT	10.7	14.4	0.01	5.1	9.3	0.06	13.6	17.3	0.05
Occult diabetes detected as FPG test ≥126 mg/dl	2.6	4.4	0.02	1.2	3.0	0.11	3.2	5.1	0.05
Occult diabetes detected as 2-h OGTT ≥200 mg/dl	8.2	12.0	0.002	5.7	9.3	0.09	9.3	13.2	0.01

Data are percent, unless otherwise indicated. *Prevalence estimates are adjusted for age, sex, race, BMI, and waist circumference. †BMI <25 kg/m². ‡BMI ≥25 kg/m².

Table 3—Association between SDB and IGM in all participants and according to weight status

IGM	Entire analytic sample (n = 2,588)		Nonoverweight (n = 679)*		Overweight/obese (n = 1,909)†	
	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)‡	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)‡	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)‡
IFG	2.0 (1.7–2.4)	1.3 (1.1–1.6)§	1.5 (1–2.3)	1.6 (1–2.5)	1.8 (1.5–2.2)¶	1.3 (1–1.6)
IGT	1.3 (1.1–1.6)	1.2 (1–1.4)	1.5 (1–2.1)	1.4 (0.9–2.1)	1.2 (1–1.5)	1.1 (0.9–1.4)
IFG plus IGT	2.0 (1.6–2.5)	1.4 (1.1–1.8)§	1.8 (0.9–3.4)	1.9 (1–3.7)	1.7 (1.3–2.3)¶	1.3 (1–1.8)
Occult diabetes detected as FPG ≥126 mg/dl	2.4 (1.6–3.6)	1.7 (1.1–2.7)	2.3 (0.8–6.6)	2.5 (0.8–8.0)	2.1 (1.4–3.3)§	1.6 (1–2.6)
Occult diabetes detected as 2-h OGTT ≥200 mg/dl	1.8 (1.3–2.3)	1.5 (1.2–2.0)§	2.0 (1.1–3.6)	1.7 (0.9–3.2)	1.6 (1.2–2.1)§	1.5 (1.1–2.0)

*BMI <25 kg/m². †BMI ≥25 kg/m². ‡Adjusted for age, sex, race, BMI, and waist circumference. §P <0.01. ||P <0.05. ¶P <0.001.

ticipants with SDB reduced the power of stratified analyses, the consistency of the point estimates between SDB and each measure of IGM in the overweight and nonoverweight groups provides evidence of an independent association between SDB and IGM. The analyses showed that SDB was also associated with unrecognized diabetes and combined IGF and IGT, a measure reported as advanced pre-diabetes (13,22).

Our findings are consistent with previous research demonstrating associations between metabolic impairments and SDB (3,4,6,7), which, however, did not as rigorously assess potential confounding by obesity. The similarity of the magnitude of associations between SDB and glucose abnormalities in the normal-weight and overweight groups, which was most significant for IFG and IGF plus IGT, suggests that SDB likely increases the risk for SDB through pathways other than through its association with adiposity. The mechanisms for these associations may relate to the often-profound physiological stresses that occur overnight with sleep apnea (intermittent hypoxia, hypercapnia, pleural pressure swings, arousal, and sleep fragmentation [19,20]). These exposures may result in a transient increase in autonomic sympathetic activity and hypothalamic-pituitary-adrenal axis hyperactivity with increased secretion of plasma cortisol and abnormalities in insulin and glucose metabolism. A potential causal relationship between SDB and IGM is consistent with animal studies (17,21) showing decreased insulin sensitivity occurring in response to intermittent hypoxia and with a human study (18) showing improved insulin sensitivity in sleep apnea patients following treatment with continuous positive airway pressure (reversing apneas and hypoxemia). Our data also extend prior work by character-

izing the association between specific indexes of IGM with SDB. Recent research (33) comparing the new revised definition of IFG (FPG ≥100 mg/dl) with IGT indicates that IFG and IGT may identify distinct groups, with different background risks (34,35). The unadjusted odds ratio for IFG was approximately twice as great in individuals with SDB compared with those without SDB. Although this association was much attenuated in adjusted analyses of data obtained in the entire analytic sample and in the overweight subgroup, the 60% increased odds of IFG observed in adjusted analyses performed in the nonoverweight subgroup suggest that normal-weight individuals with SDB are at an increased risk for experiencing defects in early insulin secretion and increased endogenous glucose output (34).

Isolated IGT, reported commonly in the setting of central obesity and considered to be a measure of peripheral insulin resistance (13,22,34), was also more prevalent in individuals with SDB. After adjusting for BMI and waist circumference, the differences in prevalence between the SDB and non-SDB group was quite modest, however, especially in overweight/obese subjects. This suggests that in a background of overweight, the predominant risk factor for isolated peripheral insulin resistance may be obesity, with little additional contribution from SDB.

Occult diabetes and combined IFG and IGT were significantly more prevalent among individuals with SDB compared with those without SDB. To the best of our knowledge, this is the first study to address the association of combined IFG and IGT with SDB. The potential clinical importance of this association relates to data that suggest that this category of IGM reflects more profound abnormalities in insulin action, insulin secretion, and en-

dogenous glucose output when compared with abnormalities in either IFG or IGT alone (13,22). Individuals with combined abnormalities have been shown to be at higher risk for an unfavorable cardiovascular risk profile, rapid development of diabetes, and premature death, compared with individuals with isolated IFG or IGT (12,13,22,34,35). The high unadjusted prevalence (18.3%) of combined glucose intolerance (IFG plus IGT) and occult diabetes (13.7%) found in the overall SDB group suggest that individuals with SDB are at special risk for diabetes and its cardiovascular complications, underscoring the need for further research addressing strategies for reducing the health risks in this population.

The strengths of the present study include recruitment of a community-based cohort, with balanced sex representation and geographic diversity, which are likely to be free of the referral biases that may occur from studies of clinic-based samples. The large sample size allowed the data to be analyzed within weight-stratified subgroups, which reduced the likelihood of residual confounding related to obesity. Data were collected following highly structured protocols, minimizing measurement error. Extensive sensitivity analyses done using different cutoffs for the RDI (5,12,15) and BMI (30), and based on the parent cohorts (Atherosclerosis Risk in Communities Study and Cardiovascular Health Study), sustain our conclusions.

The study also has limitations. The measurements of glucose impairment and sleep were based on a one-time collection, and the blood was not collected in immediate temporal proximity to the overnight sleep study. However, both of the conditions (SDB and impaired glucose metabolism) are chronic in nature, with indexes of glucose metabolism and SDB tracking

well over time. Error introduced by the lack of simultaneous collection of metabolic and polysomnographic data should, in any case, bias toward a null result. The participants' demographic characteristics, especially older age and predominantly Caucasian race, limits generalizability to younger groups or to ethnic minorities. As aging was reported as a common determinant of IFG or IGT (34), and the median age for all SDB groups was higher compared with the non-SDB groups, there is a possibility of residual confounding by age, although this is unlikely, as the extensive overlap in age distribution between groups should allow effect adjustment for age in multivariable models. Despite adjustment for both BMI and waist girth, some degree of residual confounding from differences in visceral fat, which was not directly measured, remains possible. The smaller numbers of normal-weight SDB participants reduced the power of analyses in this stratum; however, the multiple analyses showed consistency across body habitus strata and IGM definitions. In addition, given the multiple outcomes and our hypothesis, we did not extensively evaluate differential risk for IGM according to severity of SDB. Rather, we used a threshold value that is commonly used clinically in older populations to identify mild elevations in the RDI and that, in our sample, classified 48% of individuals as having SDB. It should be emphasized, however, that sensitivity analyses using alternative SDB thresholds yielded qualitatively similar results.

In summary, this study provides additional evidence that individuals with SDB have a higher prevalence of IFG, IGT, combined IFG and IGT, and occult diabetes compared with those without SDB and shows consistency of associations between SDB and each measure of IGM among normal-weight and overweight individuals. Given the high prevalence of SDB in the population (1,2), the 20–70% increased adjusted odds for IGM, abnormalities of which are associated with significant disease burden, suggests a potentially high attributable risk associated with unrecognized SDB. The results suggest potential benefits for monitoring indexes of glucose metabolism in patients with known SDB, even if they are not overweight. Further work is needed to determine the effect of SDB on progression of IGM over time, the potential clinical benefits of treating SDB as a strategy for improving IGM, and the role of systemic screening and treatment of IGM in patients with SDB for the prevention of

ischemic cardiovascular disease and premature death.

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