

**Sleep Disordered Breathing and Impaired Glucose Metabolism in Normal Weight and Overweight/Obese Individuals:
The Sleep Heart Health Study**

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Running Title: SDB and IGT/ IFG in normal and overweight/obese individuals

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ABSTRACT

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

Research Design and Methods: Cross-sectional analysis of 2,588 participants (age 52-96 years; 46% men) without known DM. SDB was defined as respiratory disturbance index ≥ 10 events/hour. IFG, IGT, occult DM, 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, gender, race, BMI and waist circumference.

Results: SDB was observed in 209 non-overweight and 1036 overweight/obese participants. SDB groups had significantly higher adjusted prevalence and adjusted odds of IFG, IFG + IGT, and occult DM. The adjusted odds ratio for all subjects was 1.3 (1.1, 1.6) for IFG, 1.2 (1.0, 1.4) for IGT, 1.4 (1.1, 2.7) for IFG + IGT, and 1.7 (1.1, 2.7) for occult DM.

Conclusion: SDB was associated with occult DM, IFG, and IFG + IGT after adjusting for age, gender, race, BMI and waist circumference. The magnitude of these associations was similar in non-overweight and overweight participants. The consistency of associations across all measures of IGM and body habitus groups, and the significant association between SDB and IFG + 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.

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 United States (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 mellitus (DM), 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 (IFG, IGT, or both) are differentially associated with SDB. Impaired fasting glucose (IFG), introduced in 1997 by the American Diabetes Association as an analog to impaired glucose tolerance (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, 22, 23, 32, 33). Glucose dysregulation with combined IFG + IGT is considered to represent an advanced stage of prediabetes, and compared to isolated IGT or isolated IFG, has a distinctly higher risk of conversion to diabetes and more severe associated comorbid illnesses (12, 29-31). Intermediate states (IFG, IGT, IFG+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 cardio-vascular disease (CVD) (28-31).

The purpose of this study was to characterize the association between SDB and each available index of IGM: IFG, IGT, combined IFG + IGT, and undiagnosed DM. 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 body mass index (BMI) less than 25 kg/m² and SDB have a higher adjusted prevalence and odds of IFG, IGT, IFG + IGT, and occult DM compared to 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 + 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). SHHS is a large multicenter cohort study designed to examine the association between SDB and CVD. 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 (24 15). 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 2h post-load 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 (CHS) (n=900), and the Atherosclerosis Risk in Communities Study, (ARIC) (n=1688). Detailed study aims and designs of these parent studies have been described elsewhere (16-17). Blood sampling was prior to the polysomnogram (PSG): 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 (Abbotsville, AU). Details on physiological parameters recorded, type of equipment used, monitoring and scoring procedures, and quality assurance are described in detail elsewhere (18). Sleep stages were assigned according to published guidelines (19,20). 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 (21). SDB was defined as RDI ≥ 10 respiratory events per hour. This was determined based on preliminary analyses, using restricted cubic splines, which suggested a 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 twelve hours, and also two hours after a 75g 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 (22), IFG was defined when fasting plasma glucose ≥ 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 (DM) by two different classification strategies: (1) FPG ≥ 126 mg/dl and (2) OGTT 2h 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) (23).

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. Body Mass Index (BMI) was calculated as weight divided by the square of the height (kg/m^2). For stratified analyses, overweight was defined according to the National Institute of Health Clinical guidelines for adults as a BMI ≥ 25 kg/m^2 (24). Waist circumference was also measured on the night of the polysomnography, using a non-stretchable tape around the minimal area over the umbilicus.

Covariates of interest included age (years), gender, and race (white/non-white, according to self-report).

STATISTICAL ANALYSIS

Descriptive statistics including median, inter-quartile 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 chi-square 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 + IGT, and occult diabetes) with SDB, the primary exposure variable, adjusted for age, gender, race, BMI, and waist circumference (24-26). 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 and 30), and IFG (100 mg/dl and 110 mg/dl), as well as to examine the consistency of associations between each parent cohort (ARIC and CHS). All analyses were performed using SAS v9.1 (SAS Institute, Inc., 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 \geq 25 kg/m²), including 30% classified as obese (BMI \geq 30 kg/m²). A wide range of RDI values was observed, with median RDI levels in the mild to moderate range (9-20 events/hr), 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 indices 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 males and older individuals. Even within each weight category, the subgroups with SDB were more likely to be male, 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 to those without SDB.

Significantly higher adjusted prevalence rates of IFG, IFG+IGT and occult diabetes were found in the SDB group when compared to 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 +

IGT, and up to one in eight with occult diabetes; the prevalence of each index of IGM was higher in the SDB subgroup compared to the subgroup without SDB. In the non-overweight SDB group, approximately one-fourth had IFG, one-third had IGT, and one-tenth was found positive for both IFG+IGT, after controlling for age, gender, race, BMI, and waist circumference. Similar to the overweight group, the adjusted prevalence rates for all indices of IGM were higher in the SDB compared to the non-SDB group, with group differences statistically significant for IFG, IFG + IGT and occult DM (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 to 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 DM 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 DM. For each index of IGM, somewhat higher adjusted point estimates were observed for SDB among the non-overweight group than the overweight/obese group, although due to the much smaller sample size, the confidence intervals 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/hour), 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, consistent with similarities of SDB associations across weight strata.

DISCUSSION

These analyses extend previous findings between SDB and glucose metabolism (3, 5-10) by rigorously assessment of potential confounding by overweight/obesity, and by exploring whether distinct indices of IGM (IFG, IGT, IFG + 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 non-overweight/obese participants 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 non-overweight 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 + IGT, a measure reported as advanced pre-diabetes (13, 28).

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+IGT, suggests that SDB likely increases 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 (29, 30). 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 showing decreased insulin sensitivity occurring in response to intermittent hypoxia (31, 32) and with a human study showing improved insulin sensitivity in sleep apnea patients following treatment with continuous positive airway pressure (reversing apneas and hypoxemia)(33).

Our data also extend prior work by characterizing the association between specific indices of IGM with SDB. Recent research (34) comparing the new revised definition of IFG (FPG \geq 100mg/dl) with IGT indicates that IFG and IGT may identify distinct groups, with different background risks (35, 36). The unadjusted odds ratio for IFG was approximately twice as great in individuals with SDB compared to 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 non-overweight subgroup suggests that normal weight individuals with SDB are at an increased risk for experiencing defects in early insulin secretion and increased endogenous glucose output (35).

Isolated IGT, reported commonly in the setting of central obesity and considered to be a measure of peripheral insulin resistance (13, 28, 35) 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 DM and combined IFG + IGT were significantly more prevalent among individuals with SDB compared to those without SDB. To the best of our knowledge, this is the first study to address the association of combined IFG +IGT with SDB. The potential clinical importance of this association relates to data that suggest this category of IGM reflects more profound abnormalities in insulin action, insulin secretion, and endogenous glucose output, when compared with abnormalities in either IFG or IGT alone (13, 28,). 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 to individuals with isolated IFG or IGT (12, 13, 28, 35, 36). The high unadjusted prevalence (18.3%) of combined glucose intolerance (IFG+IGT) and occult DM (13.7 %) found in the overall SDB group suggest 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 gender 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, 9, 10), BMI (21), and based on the parent cohorts (ARIC and CHS), 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 indices 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 a common determinant of IFG or IGT (35), and the median age for all SDB groups was higher compared to 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 which, 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 + IGT, and occult DM compared to 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 to 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 indices 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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REFERENCES

1. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 165:1217-1239, 2002.
2. Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Sleep-disordered breathing in community-dwelling elderly. *Sleep*. 1991 Dec;14(6):486-95.
3. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, and Smith PL. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am J Respir Crit Care Med* 165: 677–682, 2002.
4. Vgontzas AN, Bixler EO, Chrousos GP. Metabolic disturbances in obesity vs. sleep apnea: 2003, *Journal of internal medicine*. Vol 254, no 1 (2003 Jul): 32-44.
5. Al Delaimy WK, Manson JE, Willett WC, Stampfer MJ, Hu FB. Snoring as a risk factor for type II diabetes mellitus: a prospective study. *Am J Epidemiol* 155: 387–393, 2002.
6. De la Eva R, Baur L, Seton C, Teng A, Waters K. Obstructive sleep apnoea correlates with insulin resistance in obese children. *Am J Respir Crit Care Med* 161:891, 2000.
7. Elmasry A, Janson C, Lindberg E, Gislason T, Tageldin MA, and 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.
8. Leineweber C, Kecklund G, Akerstedt T, Janszky I, Orth-Gomer K. Snoring and the metabolic syndrome in women. *Sleep Med* 4: 531–536, 2003.
9. Punjabi NM, Ahmed MM, Polotsky VY, Beamer BA, O'Donnell CP. Sleep-disordered breathing, glucose intolerance, insulin resistance. *Resp Phys Neuro* 136: 167–178, 2003.
10. Stoohs RA, Facchini F, Guilleminault C. Insulin resistance and sleep-disordered breathing in healthy humans. *Am J Respir Crit Care Med* 154: 170–174, 1996.
11. Punjabi NM, Polotsky VY. “Disorders of glucose metabolism in sleep apnea.” *J Appl Physiol*: v. 99 issue 5, 2005, p. 1998-2007.
12. Nakamura Y, Saitoh S, Takagi S, Ohnishi H, Chiba Y, Kato N, Akasaka H, Miura T, Tsuchihashi K, Shimamoto K. Impact of abnormal glucose tolerance, hypertension and other risk factors on coronary artery disease. *Circ J*. 2007 Jan;71(1):20-5.
13. Balkau B. The DECODE study. *Diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe*. *Diabetes Metab*, 2000;26:282-286.
14. Unwin N, Shaw J, Zimmet P, Alberti KGGM: Impaired glucose tolerance and impaired fasting glycaemia: status on definition and intervention. *Diabet Med* 19:708 –723, 2002.
15. 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* 1997;20:1077–85.
16. Fried, LP; Borhani, NO; Enright, P; Furberg, CD; Gardin, JM; Kronmal, RA; Kuller LH, Manolio TA, Mittelmark MB, Newman A, O'Leary D, Psaty B, Rautaharju P, Tracy R. The Cardiovascular Health Study. *Ann Epidemiol*. 3(1); 263-276. 1991. (CHS# B00).
17. The ARIC investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am J Epidemiol*. 1989 Apr;129(4):687-702.
18. 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 Heart Health Research Group. *Sleep* 1998;21:759–67.
19. Rechtschaffen A, Kales A. A manual of standardized techniques and scoring system for sleep stages of human subjects. *Government Print Office* NIH Publication No. 204. 1968.

20. The Atlas Task Force EEG arousals: scoring rules and examples. *Sleep* 15:173-84, 1992.
21. Kushida CA, Littner MR, Morgenthaler T, Alessi CA, Bailey D, Coleman J, Friedman L, Hirshkowitz M, Kapen S, Kramer M, Lee-Chiong T, Loube DL, Owens J, Pancer JP, Wise M. Practice Parameters for the Indications for Polysomnography and Related Procedures: An Update for 2005; 499-519.
22. American Diabetes Association, Diagnostic and Classification of Diabetes. *Diabetes Care* 28: S 537-542, 2005.
23. Expert Committee on the Diagnosis and Classification of Diabetes. *DCare* 2000; 23(suppl 1):S4–20.
24. Clinical guidelines of identification, Evaluation, and Treatment of Overweight and Obesity in Adults-The evidence Report. National Institute of Health. *Obes Res* 6 Suppl 2:51s-209s, 1998.
25. Partinen M. Epidemiology of obstructive sleep apnea syndrome. *Curr Opin Pulm Med* 1:482–487, 1995.
26. 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.
27. Larsson H, Berglund G, Lindgarde F, Ahren B: Comparison of ADA and WHO criteria for diagnosis of diabetes and glucose intolerance. *Diabetologia* 41:1124 –1125, 1998.
28. Weyer C, Bogardus C, Pratley E. Metabolic Characteristics of Individuals with Impaired Fasting Glucose and/or Impaired Glucose Tolerance, *Diabetes*, 48, Nov,1999:2197-2203.
29. Dimsdale JE, Coy T, Ziegler MG, Ancoli-Israel S, Clausen J. The effect of sleep apnea on plasma and urinary catecholamines. *Sleep* 1995;18(5):377-81.
30. Narkiewicz K, van de Borne PJ, Cooley RL, Dyken ME, Somers VK. Sympathetic activity in obese subjects with and without obstructive sleep apnea. *Circulation* 1998;98(8):772-6.
31. Iiyori N, Alonso LC, Li J, Sanders MH, Garcia-Ocana A, O'Doherty RM, Polotsky VY, O'Donnell . Intermittent hypoxia causes insulin resistance in lean mice independent of autonomic activity. *Am J Respir Crit Care Med*. 2007 Apr 15;175(8):851-752.
32. Cheng, N., W. Cai, M. Jiang, and S. Wu.. Effect of hypoxia on blood glucose, hormones, and insulin receptor functions in newborn calves. *Pediatr Res* 1997. 41(6):852-6.
33. Harsch IA, Schahin SP, Radespiel-Troger M, Weintz O, Jahreiss H, Fuchs FS, Wiest GH, Hahn EG, Lohmann T, Konturek PC, Ficker JH. Continuous Positive Airway Pressure Treatment Rapidly Improves Insulin Sensitivity in Patients with Obstructive Sleep Apnea Syndrome. *Am J Respir Crit Care Med* 2004;169(2):156-62.
34. Vaccaro O, Riccardi G. Changing the definition of impaired fasting glucose: impact on the classification of individuals and risk definition. *Diabetes Care* 28:1786–1788, 2005.
35. Thomas G N, Schooling C M, McGhee S M, Ho I S Y, Cheung B M Y, Wat N M, Janus E D, Lam T H. Identification of factors differentially associated with isolated impaired fasting glucose and isolated post-load impaired glucose tolerance: the Hong Kong Cardiovascular Risk Factor Study. *Eur J Endocrinol*. 155 623–632, 2006.
36. Abdul-Ghani MA, Jenkinson CP, Richardson DK, Tripathy D, DeFronzo RA. Insulin Secretion and Action in Subjects With Impaired Fasting Glucose and Impaired Glucose Tolerance Results From the Veterans Administration Genetic Epidemiology Study. *Diabetes*. Vol. 55, 1430-1435, 2006.

TABLE 1. Subject Characteristics*: In the Analytic Sample and According to Weight and SDB[†] Status:

* Median and Interquartile Range for continuous variables.

	Total Participants (N=2588)	Non-overweight [†] (N=679)			Overweight/Obese [‡] (N=1909)		
		No SDB [§] (N=470)	SDB [§] (N=209)	p-value	No SDB [§] (N=873)	SDB [§] (N=1036)	p-value
Age	67 (60-75)	66 (59-75)	75 (67-80)	< 0.0001	66 (59-74)	68 (61-74)	0.001
Male Gender	1196 (46.2%)	136 (28.9%)	107 (51.2%)	<.0001	320 (36.7%)	633 (61.1%)	< 0.0001
White Race	2428 (93.8%)	449 (95.5%)	196 (93.8%)	0.330	813 (93.1%)	970 (93.6%)	0.70
FPG (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 ^{††} (cm)	98 (91-106)	86 (80-92)	89 (82-93)	0.008	100 (94-106)	104 (98-112)	< 0.0001

[†] BMI < 25kg/m²[‡] BMI ≥ 25kg/m²[§] SDB: Sleep Disordered Breathing^{||} FPG is Fasting Plasma Glucose Test[¶] OGTT: Two Hour Oral Glucose Tolerance Test[#] RDI: Respiratory Disturbance Index: respiratory events per hours each associated with ≥3% decreases in oxyhemoglobin saturation^{**} BMI: Body Mass Index^{††} Waist: Waist Circumference

TABLE 2. Adjusted prevalence* of impaired glucose metabolism in all participants and according to weight and SDB^{||} status:

	Total Participants (N=2588)			Non-overweight [‡] (N=679)			Overweight/Obese ^δ (N=1909)		
	No SDB (N=1343)	SDB (N=1245)	p-value	No SDB (N=470)	SDB (N=209)	p-value	No SDB (N=873)	SDB (N=1036)	p-value
IGM [†]									
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 [¶] +IGT [#]	10.7%	14.4%	0.01	5.1%	9.3%	0.06	13.6%	17.3%	0.05
DM ^{**}	2.6%	4.4%	0.02	1.2%	3.0%	0.11	3.2%	5.1%	0.05
DM ^{††}	8.2%	12.0%	0.002	5.7%	9.3%	0.09	9.3%	13.2%	0.01

* Prevalence estimates are adjusted for age, gender, race, BMI, and waist circumference.

[†] IGM: Impaired Glucose Metabolism

[‡] BMI < 25kg/m²

^δ BMI ≥ 25kg/m²

^{||} SDB is Sleep Disordered Breathing

[¶] IFG is Impaired Fasting Glucose

[#] IGT is Impaired Glucose Tolerance

^{**} DM is occult diabetes mellitus detected as (Fasting Plasma Glucose Test ≥ 126 mg/dl)

^{††} DM is occult diabetes mellitus detected (Two Hour Oral Glucose Tolerance Test ≥ 200 mg/dl)

TABLE 3. Association between SDB and impaired glucose metabolism in all participants and according to Weight Status

	Entire Analytic Sample (N=2588)		Non-overweight [‡] (N=679)		Overweight/Obese ^δ (N=1909)	
	Unadjusted OR ^{‡‡}	Adjusted OR ^{‡‡}	Unadjusted OR ^{‡‡}	Adjusted OR ^{‡‡}	Unadjusted OR ^{‡‡}	Adjusted OR ^{‡‡}
IGM [†]						
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 [¶] + 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)*
DM ^{**}	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)*
DM ^{††}	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)*

[†] IGM: Impaired Glucose Metabolism

[‡] BMI < 25kg/m²

^δ BMI ≥ 25kg/m²

^{||} Adjusted for age, gender, race, BMI, and waist circumference

[¶] IFG is Impaired Fasting Glucose

[#] IGT is Impaired Glucose Tolerance

^{**} DM is occult diabetes mellitus detected as (Fasting Plasma Glucose Test ≥ 126 mg/dl)

^{††} DM is occult diabetes mellitus detected (Two Hour Oral Glucose Tolerance Test ≥ 200 mg/dl)

^{‡‡} P-value <0.05*, <0.01**, <0.001*** and All Odd Ratios (OR) are done at a 95% Confidence Interval (CI)