CHEST

Original Research

SLEEP DISORDERS

Sleep Apnea and Glucose Metabolism

A Long-term Follow-up in a Community-Based Sample

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Background: **It has been suggested that sleep-disordered breathing (SDB) is a risk factor for diabetes, but long-term follow-up studies are lacking. The aim of this community-based study was to analyze the influence of SDB on glucose metabolism after > 10 years.**

Methods: **Men without diabetes (N = 141; mean age, 57.5 years) were investigated at baseline, including whole-night respiratory monitoring. After a mean period of 11 years and 4 months, they were followed up with an interview, anthropometric measurements, and blood sampling. Insulin resistance was quantified using the homeostasis model assessment of insulin resistance (HOMA-IR). ΔHOMA-IR was calculated as (HOMA-IR at follow-up − HOMA-IR at baseline). An oral glucose tolerance test was performed on 113 men to calculate the insulin sensitivity index.**

Results: **The mean apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) at baseline were 4.7 and 3.3, respectively. At follow-up, 23 men had diabetes. An ODI > 5 was a predictor of developing diabetes (OR, 4.4; 95% CI, 1.1-18.1, after adjusting for age, BMI, and hypertension at baseline and ΔBMI and years with CPAP during follow-up). The ODI was inversely related to the insulin sensitivity index at follow-up ($r = -0.27$, $P = .003$). A deterioration in HOMA-IR was significantly related to all variables of SDB (AHI, AHI > 5; ODI, ODI > 5; minimum arterial oxygen saturation), even when adjusting for confounders. When excluding the variable years with CPAP from the multivariate model, all associations weakened.**

Conclusions: **SDB is independently related to the development of insulin resistance and, thereby, the risk of manifest diabetes mellitus.**

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Abbreviations: AHI = apnea-hypopnea index; FPG = fasting plasma glucose; HOMA-IR = homeostasis model assessment of insulin resistance; IFG = impaired fasting glucose; ISI = insulin sensitivity index; ODI = oxygen desaturation index; OGTT = oral glucose tolerance test; OSA = obstructive sleep apnea; SDB = sleep-disordered breathing

Sleep-disordered breathing (SDB) and diabetes mellitus are both common diseases that share several risk factors. Like diabetes, untreated sleep apnea is associated with hypertension[1] and a high incidence of cardiovascular events.[2] It has been suggested that one link between SDB and diabetes in causing morbidity is insulin resistance. In cross-sectional studies, sleep apnea is associated with insulin resistance and type 2 diabetes, independent of obesity and other confounders.[3-9]

In several studies, the observation that sleep debt[10] and hypoxemia[11] are independently associated with glucose intolerance and insulin resistance suggests a causal link between SDB and abnormal glucose metabolism. However, even if studies have shown that self-reported snoring and incident diabetes are associated,[12,13] the influence of objectively measured sleep apnea on disordered glucose metabolism is less clear because prospective studies have produced conflicting results.[6,14-16] Prospective studies have had < 4 years of follow-up; furthermore, in previous community-based studies, the treatment of SDB has not been accounted for. The aim of the present study was to analyze the influence of SDB at baseline on glucose metabolism after a mean follow-up period of ≥ 11 years in a community-based sample of men, also adjusting for possible confounders, including treatment of SDB.

Materials and Methods

Population

From a population-based sample of men who had responded to postal questionnaires in 1984 and 1994, an age-stratified sample of 232 underwent a whole-night sleep recording during 1996 to 1998 in a study of snoring and SDB in individuals with and without hypertension.[17] Their mean age was 60.6 years (range, 43-82 years), and one-half were being treated for hypertension. In 2008, 43 of the men had died, and the remaining 189 men were invited to this longitudinal study. In all, 156 (82.5%) agreed to participate in the follow-up. The reasons for not participating were disease (malignancy, n = 2; Alzheimer disease, n = 1; stroke, n = 2; unspecified advanced disease, n = 4); old age (n = 3); living abroad or at a long distance from Uppsala, Sweden (n = 2); busy at work (n = 3); or not specified (n = 16). Fifteen of the 156 men fulfilled the diagnostic criteria for diabetes mellitus already at baseline and were excluded. The study population, therefore, comprised 141 men. A 75-g oral glucose tolerance test (OGTT) was performed in 113 (80%). The exclusion criteria for performing the OGTT in 2008 were known diabetes mellitus at the interview (n = 14). In addition, men with a fasting plasma glucose (FPG) level of ≥ 7.0 mmol/L (n = 9) or those who refused to participate in the OGTT (n = 5) were excluded. The study design is presented in Figure 1.

Investigations at Baseline, 1996 to 1998

A medical history that included symptoms of SDB, medication, and current and previous diseases was taken in an interview at the sleep clinic conducted by an experienced nurse. Daytime sleepiness was assessed using the Epworth Sleepiness Scale. Whole-night respiratory monitoring was performed in the subjects' homes using the Eden Trace II (Model 3711; Eden Tec Corp) multichannel recording system. The monitoring system is a portable, four-channel recorder measuring nasal and oral airflow (thermocouple), chest wall impedance, oxygen saturation (finger pulse oximetry), snoring sounds, and body position.[18] Desaturation was defined as a decrease in oxygen saturation of at least 4%. Apnea was defined as a cessation of oronasal airflow for at least 10 s and hypopnea as a ≥ 50% reduction in oronasal airflow for at least 10 s followed by a desaturation or a compensatory increase in thoracoabdominal impedance of at least 50%. All events were scored manually.[17]

The subjects returned the following morning after fasting for an examination. Weight and height were measured and BMI was calculated. Waist circumference was measured midway between the lower rib margin and the anterior superior iliac spine.

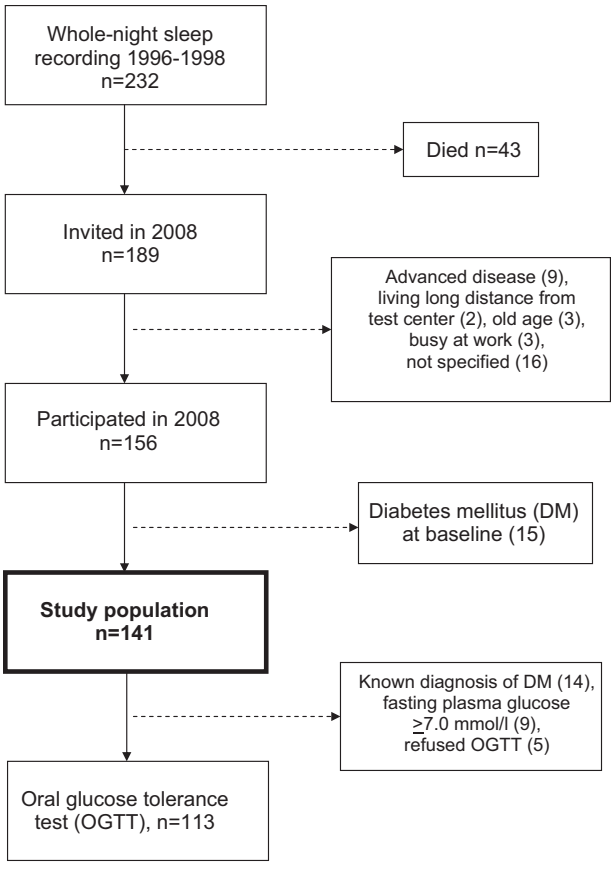

Figure 1. Study design.

Procedure at Follow-up

The follow-up visits took place between February and November 2008. The mean interval between the baseline investigation and the follow-up was 11 years and 4 months (range, 125-148 months). The same procedure as at baseline was repeated, except for the sleep recording. The differences in BMI and waist circumference between the baseline investigation and the follow-up were calculated.

Analyses of Glucose Metabolism

Both at baseline and at the follow-up, a fasting venous blood sample was taken for the determination of plasma glucose and serum insulin. Insulin resistance was quantified using the homeostasis model assessment of insulin resistance (HOMA-IR) and was calculated as (blood glucose × serum insulin)/22.5.[19] Diabetes was defined as answering yes to the question, "Do you have diabetes"; attending regular visits for diabetes control; and having an FPG of ≥ 7.0 mmol/L. Impaired fasting glucose (IFG) was defined as an FPG of > 6.1 and < 7.0 mmol/L according to the World Health Organization.[20]

All men without diabetes and with an FPG < 7.0 mmol/L were invited for an OGTT within the next month. After an overnight fast, the men received 75 g of glucose in 300 mL of water, and venous blood samples for measurements of plasma glucose and serum insulin levels were taken at 0, 30, 60, 90, and 120 min. Insulin sensitivity was expressed as the insulin sensitivity index

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(ISI) developed by Matsuda and DeFronzo,[21] which is based on FPG, fasting plasma insulin, and mean glucose and insulin concentrations during the OGTT. The formula for ISI was 10,000/[(FPG × fasting plasma insulin × mean OGTT glucose concentration × mean OGTT insulin concentration)] ^ 0.5). This index has been shown to provide a good estimate of whole-body insulin sensitivity and correlates well with the euglycemic insulin clamp.

Statistical Analysis

Statistical analysis was performed using Stata 10.0 (Stata Corp). The continuous variables that were not normally distributed (apnea-hypopnea index [AHI], oxygen desaturation index [ODI]) were log-transformed, and the data are presented as the geometric mean with 95% CI. An unpaired *t* test, a nonparametric (Mann-Whitney) test, or the χ^2 test was applied to compare baseline data between groups. Correlations between continuous variables were calculated using linear regression. For the simultaneous evaluation of more than two variables, multiple logistic regression analysis was performed, the results of which are presented as an adjusted OR and 95% CI. Because there was a close relationship between BMI and waist circumference ($r^2 = 0.85$, $P < .0001$), only BMI was used in the multiple regression analysis. The null hypothesis was rejected at a level of $P < .05$.

A new variable was created to measure the change in HOMA-IR over time: ΔHOMA-IR was calculated as (HOMA-IR at follow-up − HOMA-IR at baseline). The 75th percentile of this difference was then used as a cutoff point to define those men who had the most severe impairment of insulin sensitivity.

The study was approved by the Ethics Committee at the Medical Faculty at Uppsala University (approval number Dnr 2007/098). All participants gave informed consent.

Results

At the follow-up, 23 men (16.3%) fulfilled the criteria for diabetes mellitus. Eleven were taking oral antidiabetic drugs and one in combination with insulin. The characteristics of the participants and differences between those with and without incident diabetes are presented in Table 1. The men who had developed diabetes were of a similar age and had similar smoking habits to the remaining participants but generally were more obese and more often had hypertension. The groups did not significantly differ in weight gain over time, although the participants who fulfilled the diagnostic criteria for diabetes at follow-up had somewhat impaired glucose metabolism already at baseline and slightly lower serum high-density lipoprotein cholesterol and higher serum triglyceride levels.

In the group that had developed diabetes, men with sleep apnea at baseline were overrepresented, whereas the level of daytime sleepiness did not differ between the groups (Table 2). Among the 113 men who underwent an OGTT, there was also an association between ODI at baseline and ISI at follow-up (Fig 2), although there was no significant association between the AHI and ISI ($r = -0.13$, $P = .2$). During the follow-up period, nine men had been treated with CPAP for a mean period of 9.3 years (range, 3-12 years). No participant had undergone oral surgery between baseline and follow-up.

SDB at baseline was associated with diabetes at the follow-up. When also adjusting for age, BMI, and hypertension at baseline and ΔBMI and CPAP treatment during follow-up, the ORs for all the variables of SDB (apart from minimum arterial oxygen saturation) increased, although the association with diabetes only remained significant for an ODI > 5 at baseline

Table 1—*Characteristics of the Population at Baseline and Differences Between the Groups With and Without Diabetes at Follow-up*

Characteristics	Total Population (N = 141)	Diabetes at Follow-up		
		No (n = 118)	Yes (n = 23)	*P* Value
Age	57.5 (56.1-58.9)	57.5 (56.0-59.0)	57.4 (53.5-61.5)	.99
BMI	26.9 (26.3-27.4)	26.4 (25.8-27.0)	29.3 (27.7-31.1)	.0002
BMI ≥ 30 kg/m²	26 (18)	16 (14)	10 (43)	.001
ΔBMI[a]	0.7 (0.3-0.7)	0.6 (0.2-0.9)	1.0 (0.0-2.1)	.8
Waist circumference	99.4 (97.9-100.9)	98.2 (96.6-99.7)	105.9 (101.6-110.4)	.0002
ΔWaist circumference[a]	3.5 (2.5-4.6)	3.4 (2.3-4.6)	3.8 (0.9-6.8)	.6
Hypertension	65 (46)	47 (39)	16 (70)	.009
Current smoker	9 (6)	8 (7)	1 (4)	.6
Previous smoker	60 (43)	49 (42)	11 (48)	.6
Impaired fasting plasma glucose	10 (7.1)	3 (2.5)	9 (39)	< .0001
Fasting serum insulin, mU/L	8.2 (7.6-8.9)	7.6 (7.1-8.2)	11.8 (9.5-14.8)	< .0001
HOMA-IR	1.9 (1.8-2.1)	1.7 (1.6-1.9)	3.9 (3.2-4.9)	< .0001
Serum cholesterol, mmol/L	5.5 (5.3-5.7)	5.5 (5.3-5.7)	5.5 (5.1-5.8)	.8
Serum HDL cholesterol, mmol/L	1.2 (1.2-1.3)	1.3 (1.2-1.3)	1.0 (0.9-1.2)	.0007
Serum LDL cholesterol, mmol/L	3.6 (3.5-3.8)	3.6 (3.4-3.8)	3.6 (3.2-4.0)	.9
Serum triglycerides, mmol/L	1.2 (1.1-1.3)	1.1 (1.0-1.2)	1.5 (1.3-1.9)	.006

Data are presented as geometric mean (95% CI) or No. (%), unless otherwise indicated. HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment of insulin resistance; LDL = low-density lipoprotein.
[a]Arithmetic mean (95% CI).

Table 2—*Prevalence of Sleep-Disordered Breathing at Baseline and Differences Between the Groups With and Without Diabetes at Follow-up*

Variable	Total Population (N = 141)	Diabetes at Follow-up		
		No (n = 118)	Yes (n = 23)	*P* Value
AHI	4.7 (3.8-5.6)	4.7 (3.8-5.7)	5.5 (3.8-8.0)	.3
AHI > 5	71 (50)	55 (47)	16 (70)	.04
ODI	3.3 (2.7-4.0)	4.0 (2.8-4.2)	4.9 (3.4-7.2)	.03
ODI > 5	53 (38)	40 (34)	13 (57)	.04
$MinSaO_2$	84.1 (83.0-85.2)	84.5 (83.2-85.8)	81.9 (79.7-84.1)	.08
ESS score	5.6 (5.0-6.3)	5.8 (5.1-6.5)	5.0 (3.8-6.6)	.5
ESS > 10	34 (24)	31 (27)	3 (13)	.2

Data are presented as geometric mean (95% CI) or No. (%). AHI = apnea-hypopnea index; ESS = Epworth Sleepiness Scale; $minSaO_2$ = minimum arterial oxygen saturation; ODI = oxygen desaturation index.

(Table 3). When further adding IFG at baseline to the model, the adjusted OR for an ODI > 5 decreased to 3.2 (95% CI, 0.7-14.2; $P = .1$), whereas the corresponding OR for an AHI > 5 was 4.0 (95% CI, 0.8-18.6; $P = .08$).

There was an independent relationship between SDB at baseline and a low ISI at follow-up (Table 4). When also adding IFG at baseline to the model, the relationship between ODI and an ODI > 5 remained significantly related to a low ISI (OR, 8.4 [95% CI, 1.7-41.1] and 8.7 [95% CI, 2.1-35.3], respectively). Additionally, AHI (OR, 4.9; 95% CI, 1.1-21.4) and an AHI > 5 (OR, 7.9; 95% CI, 2.1-29.8) at baseline were predictors of a low ISI, independent of IFG at baseline. If IFG was replaced by HOMA-IR at baseline, the results did not change significantly other than that the association with AHI was no longer significant (OR, 4.7; 95% CI, 0.8-28.2).

The mean HOMA-IR was 1.9 (95% CI, 1.8-2.1) at baseline and 2.4 (95% CI, 2.1-2.8) at follow-up, and the cutoff point for the highest quartile of individual changes was 1.42. A deterioration in HOMA-IR was significantly related to all measured variables of SDB, even when adjusting for confounders (Table 5). Excluding the participants who fulfilled the criteria for diabetes in 2008 (n = 23) or adding IFG at baseline to the models did not significantly change these results. However, when analyzing the data without adjusting for the variable years with CPAP treatment, all the ORs became lower, and only the association with AHI > 5 remained significant (Fig 3).

When replacing BMI and ΔBMI with waist circumference and Δwaist circumference in all models, the results of the multivariate analysis did not significantly change other than that the association between an ODI > 5 and diabetes was no longer significant (OR, 3.8; 95% CI, 0.98-14.4). There was no significant interaction with hypertension or a BMI ≥ 30 kg/m² at baseline in any of the models.

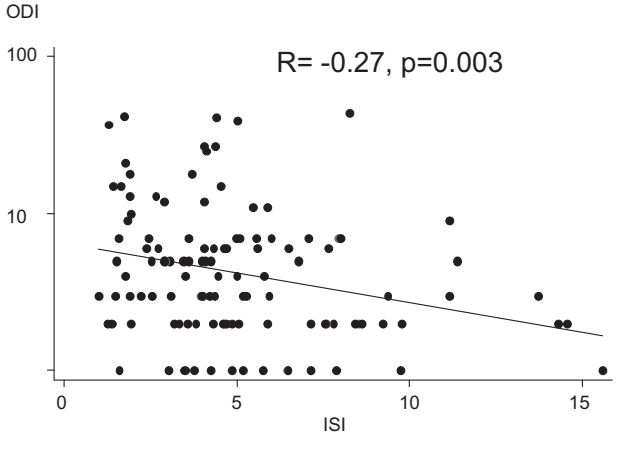

FIGURE 2. ISI at the follow-up by ODI at baseline (logarithmic scale). ISI = insulin sensitivity index; ODI = oxygen desaturation index.

DISCUSSION

The results of this follow-up study demonstrate that SDB has negative effects on glucose metabolism and insulin sensitivity. At follow-up after > 11 years, all the analyzed variables of SDB were significant, independent predictors of a low ISI and of impairment in insulin sensitivity. SDB reached borderline significance for the development of manifest diabetes.

Cross-sectional studies have clearly shown a link between SDB and abnormal glucose metabolism,[3-9] but the evidence supporting a role for sleep apnea in the pathways leading to the development of type 2 diabetes has been limited. The results of the few prospective studies that have been performed have been conflicting. The risk of developing diabetes over a 4-year period among participants in the Wisconsin Sleep Cohort did not differ significantly between the subjects with an AHI ≥ 15 and those with an AHI < 5 (OR, 1.62; 95% CI, 0.7-3.6) when adjusting for age, sex, and body habitus.[6] In contrast, among Japanese community residents who were investigated by pulse oximetry and followed up after a median period of 3 years, there was an independent relationship between

Table 3—*Associations Between Variables of Sleep-Disordered Breathing at Baseline and Diabetes Mellitus at Follow-up*

	Diabetes at Follow-up (N = 141)			
Variable	Unadjusted Model	*P* Value	Multivariate Adjusted Model[a]	*P* Value
AHI[b]	1.8 (0.6-5.6)	.3	2.5 (0.5-13.6)	.3
AHI > 5	2.6 (1.003-6.8)	.04	4.2 (0.9-18.3)	.06
ODI[b]	3.3 (1.1-10.0)	.03	4.4 (0.8-25.0)	.1
ODI > 5	2.5 (1.02-6.3)	.04	4.4 (1.1-18.1)	.04
$MinSaO_2$	0.94 (0.88-1.003)	.06	0.94 (0.86-1.04)	.2

Data are presented as OR (95% CI). See Table 2 legend for expansion of abbreviations.
[a]Adjusted for age, BMI, and hypertension at baseline and ΔBMI and years with CPAP treatment of sleep apnea during follow-up.
[b]Calculated as log-transformed values.

intermittent hypoxia during sleep and the incidence of diabetes. The adjusted hazard ratio for developing type 2 diabetes was 1.69 (95% CI, 1.04-2.76) among those with an ODI3% of ≥ 15 compared with persons with no intermittent hypoxia.[16] Additionally, in an Australian population, moderate to severe apnea was related to incident diabetes, even after adjustments for confounders; however, the number of subjects who developed diabetes was only nine and the CI was wide (OR, 13.4; 95% CI, 1.6-114.1).[14] Treatment of SDB during the follow-up period was not adjusted for any of these community-based, prospective studies.

The results from the present study are in accordance with the clinic-based study presented by Botros et al,[15] who followed 544 patients referred for the evaluation of SDB and free of diabetes at baseline. During a mean follow-up period of 2.7 years, 61 patients were given a diagnosis of diabetes, and sleep apnea at baseline was significantly related to incident diabetes, also after adjusting for confounders. In the cited study, the probability of incident diabetes was attenuated for those who used regular CPAP compared with those who did not. Although the effect of CPAP treatment was not the main focus of the present study and the number of effectively treated subjects was low, all associations between SDB and impairment in glucose metabolism strengthened when CPAP treatment was added to the multivariate analyses.

In studies designed to analyze the effect of CPAP treatment on glucose metabolism and insulin resistance, a positive effect has been reported by some[22,23] but not by others.[24,25] In these studies, the effects on glucose metabolism have been evaluated within days or up to a few months. The limited duration of the randomized controlled studies could partly account for the nonsignificant effect of CPAP treatment on glucose metabolism reported in many studies.[26]

As expected, men who had developed diabetes at the follow-up had characteristic changes in known risk factors for the development of diabetes already at baseline. However, the association between SDB at baseline and a low insulin sensitivity at follow-up could not be explained by IFG or HOMA-IR at baseline. Furthermore, a deterioration in HOMA-IR was significantly related to all measured variables of SDB, even when confounders were taken into account.

The pathophysiologic mechanisms by which SDB may impair glucose tolerance and increase insulin resistance are not fully understood.[26] In healthy humans, acute sleep deprivation can cause a state of glucose intolerance,[27] and SDB might affect the metabolism indirectly by reducing the quantity of sleep, quality of sleep, or both. However, in the present

Table 4—*Associations Between Sleep-Disordered Breathing at Baseline and the ISI at Follow-up Among Men Who Underwent the Oral Glucose Tolerance Test*

	25th Percentile ISI (n = 113)			
Variable	Unadjusted Model	*P* Value	Multivariate Adjusted Model[a]	*P* Value
AHI[b]	2.4 (0.8-7.0)	.1	5.0 (1.2-21.8)	.03
AHI > 5	2.4 (0.97-6.0)	.06	6.6 (1.8-23.9)	.004
ODI[b]	4.3 (1.5-12.6)	.007	8.7 (1.8-43.1)	.008
ODI > 5	2.7 (1.1-6.6)	.03	7.1 (1.8-27.4)	.004
$MinSaO_2$	0.9 (0.9-1.002)	.06	0.93 (0.86-1.02)	.1

Data are presented as OR (95% CI). The 25th percentile of ISI was used as a cutoff point to define those men who had a low ISI. ISI = insulin sensitivity index. See Table 2 legend for expansion of other abbreviations.
[a]Adjusted for age, BMI, and hypertension at baseline and ΔBMI and years with CPAP treatment of sleep apnea during follow-up.
[b]Calculated as log-transformed values.

Table 5—*Associations Between Sleep-Disordered Breathing and ΔHOMA-IR During Follow-up*

	75th Percentile ΔHOMA-IR (N = 141)			
Variable	Unadjusted Model	*P* Value	Multivariate Adjusted Model[a]	*P* Value
AHI[b]	2.7 (0.98-7.4)	.054	4.9 (1.3-18.8)	.02
AHI > 5	2.4 (1.04-5.4)	.04	4.4 (1.5-13.0)	.007
ODI[b]	4.3 (1.5-11.8)	.005	5.2 (1.3-20.9)	.02
ODI > 5	2.3 (1.03-5.2)	.04	3.2 (1.1-9.4)	.03
$MinSaO_2$	0.93 (0.88-0.99)	.02	0.92 (0.85-0.99)	.04

Data are presented as OR (95% CI). The 75th percentile of ΔHOMA-IR was used as a cutoff point to define those men who had the most severe impairment of insulin sensitivity. See Table 1 and 2 legends for expansion of abbreviations.
[a]Adjusted for age, BMI, and hypertension at baseline and ΔBMI and years with CPAP treatment of sleep apnea during follow-up.
[b]Calculated as log-transformed values.

community-based study, the participants in general were not sleepy, and the level of daytime sleepiness was not related to diabetes at follow-up, suggesting explanations other than sleep deprivation.

In experimental animals, intermittent hypoxia increases insulin resistance,[28] and exposure to hypoxic conditions increases insulin resistance in both human and murine adipocytes by the inhibition of insulin receptor phosphorylation.[29] Moreover, human experiments have shown that acute altitude hypoxia induces a significant decrease in insulin sensitivity.[30] The hypothesis that hypoxia is involved is supported by the present observations because the severity of intermittent hypoxia during the night (ODI) independently predicted impaired glucose metabolism. The intermittent hypoxemia and reoxygenation accompanying obstructive sleep apnea (OSA) may trigger the formation of inflammatory cytokines,[31] which promote peripheral insulin resistance.[32] Clinic-based studies have reported higher levels of the inflammatory cytokines tumor necrosis factor-α and IL-6 in patients with OSA syndrome compared with control subjects.[33] In addition, the deoxygenation and reoxygenation cycles in OSA provide an environment promoting oxidative stress,[31] which, in combination with hyperglycemia, may enhance the formation of advanced glycation end products.[34] Finally, arousals accompanying OSA increase nocturnal sympathetic activity. Increased sympathetic nervous system activity can influence glucose metabolism by increasing glycogen breakdown and gluconeogenesis and is known to be associated with insulin resistance.[35]

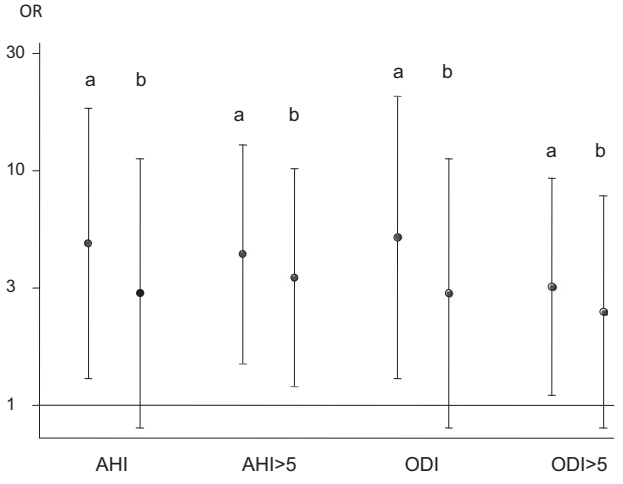

FIGURE 3. OR and 95% CI (logarithmic scale) for associations between sleep-disordered breathing and high impairment of insulin resistance defined as the 75th percentile of the change in homeostasis model assessment of insulin resistance. The independent variables are presented on the *x* axis, and log-transformed values are used for AHI and ODI. The "a" indicates adjustment for age, BMI, and hypertension at baseline and ΔBMI and years with CPAP treatment during follow-up. The "b" indicates adjustment for the same confounders as in "a" except treatment with CPAP was excluded from the model. AHI = apnea-hypopnea index. See Figure 2 legend for expansion of other abbreviation.

The strengths of this study include being community based, having a long follow-up period, and using several diverse end points of glucose metabolism, including both the ISI and the change in insulin resistance over time. The most important limitation is that polysomnography was not used, so the sleep time could only be estimated. On the other hand, identical criteria were used to estimate sleep time for all participants and the same scorer, blinded to the recorded participants, evaluated all sleep studies. Therefore, it appears unlikely that the systematic overestimation or underestimation of AHI or ODI would have markedly influenced the results. The information on the exact time course of development of diabetes mellitus in relation to SDB is somewhat limited because of the lack of interim assessments, including sleep recordings during the follow-up period. Further, this study was in men, and the generalizability of the results must await studies in women. Despite these limitations, this longitudinal study provides strong support for an independent relationship between SDB and the future impairment of glucose tolerance.

We conclude that SDB is independently related to the development of insulin resistance and, thereby, the risk of manifest diabetes mellitus. Although the

study indicates that CPAP treatment can modify this risk, there is a need for randomized controlled interventional trials to confirm this.

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Dr Lindberg: contributed to the study concept and design; data acquisition, analysis, and interpretation; drafting and revision of the manuscript; and review and approval of the final manuscript.
Dr Theorell-Haglöw: contributed to the study concept and design, data acquisition and interpretation, drafting and revision of the manuscript, and review and approval of the final manuscript.
Dr Svensson: contributed to the data acquisition, drafting and revision of the manuscript, and review and approval of the final manuscript.
Dr Gislason: contributed to the study concept and design, data interpretation, drafting and revision of the manuscript, and review and approval of the final manuscript.
Dr Berne: contributed to the study concept and design, data interpretation, drafting and revision of the manuscript, and review and approval of the final manuscript.
Dr Janson: contributed to the study concept and design; data acquisition, analysis, and interpretation; drafting and revision of the manuscript; and review and approval of the final manuscript.
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