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Obstructive sleep apnea is associated with decreased insulin sensitivity in women

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ABSTRACT

Introduction: The aim of this study was to assess associations between obstructive sleep apnea and insulin sensitivity in a population-based sample of women.

Methods: Women aged 20-70 years (n=400) underwent a full-night polysomnography, fasting blood sampling, measurement of anthropometric variables and oral glucose tolerance test with measurement of the insulin response (n=358). The apnea-hypopnea-index was calculated from the results of the polysomnography. From the results of the oral glucose tolerance test, an insulin sensitivity index was calculated.

Results: Women with an apnea-hypopnea-index <5 (n=119) had a mean insulin sensitivity index of 8.3 (±3.8), whereas women with apnea-hypopnea-index ≥30 (n=34) had a mean insulin sensitivity index of 6.2 (±4.0) (p for trend<0.0001). Nocturnal minimal saturation was independently associated with decreased insulin sensitivity when controlling for age, waist-hip-ratio, level of physical activity, smoking and alcohol consumption (β=0.07; 95% confidence interval (CI) 0.004, 0.14). When adjusting for confounders, the apnea-hypopnea-index was associated with increased fasting and two hour insulin levels (β=0.56; 95% CI 0.14, 0.99 and β=3.38; 95% CI 0.28, 6.47, respectively).

Conclusions: Obstructive sleep apnea was independently associated with decreased insulin sensitivity in this population-based sample of women.

Word count: 187

INTRODUCTION

The obstructive sleep apnea syndrome and diabetes mellitus are both closely related to obesity[1]. Studies have indicated an independent association between the two conditions, as treatment of obstructive sleep apnea syndrome patients with continuous positive airway pressure results in an improvement in glucose metabolism[2-4] although there are also conflicting studies[5, 6]. Furthermore, in population-based studies an independent association between self-reported snoring, a common symptom of sleep-disordered breathing, and incident diabetes has been reported in both men[7] and women[8]. In non-obese men self-reported snoring was also associated with decreased insulin sensitivity[9].

Studies on the impact of measured obstructive sleep apnea (OSA), however, have focused primarily on clinical patients with obstructive sleep apnea syndrome[2, 10-12]. The role of sleep related breathing disorder as a risk factor for diabetes mellitus in a general female population is less clear. Impaired insulin sensitivity is one of the major defects underlying development of type 2 diabetes mellitus. The aim of the study was therefore to assess the relationships between OSA and insulin sensitivity in a population-based sample of women.

METHODS

Population

The second phase of the population-based study "Sleep and Health in women" was conducted between 2002 and 2004. In the first phase randomly selected women (ages ≥20 years) from the population registry of the city of Uppsala, Sweden, were sent a questionnaire on sleep disturbances and somatic disorders and 7,051 (71.6%) of the women responded[13]. Figure 1

shows a flow chart of the study design. In the questionnaire snoring was assessed by the question: “How often do you snore loudly and disturbingly?” The response options were ‘never’ (1), ‘seldom’ (2), ‘sometimes’ (3), ‘often’ (4) and ‘very often’ (5). Based on the women’s response to this question, the participants were categorized into non-snorers (scores 1-3; n=6,515) and snorers (scores 4-5; n=536). In the second phase of the study a sample of 400 women were selected from the responders in the first phase aged < 70 years (n=6,112). Of the 400 women, 230 were selected randomly from the snorers and 170 were selected randomly from the whole group. The sampling was conducted this way in order to get an over-sampling of snorers. Subjects who were expected not to manage carrying out the ambulatory recordings due to severe somatic or psychiatric disease were excluded.

Polysomnography

All women underwent a whole night polysomnography in their own home or at the patient’s hotel of the hospital, using the ambulatory system EMBLA (Flaga Inc., Iceland). Sixteen channels were recorded and included two electro-encephalography leads (C3-A2 and C4-A1), two electro-oculography leads and three electromyography leads (submental, and left and right anterior tibialis muscles). In addition, two airflow leads (oronasal thermistor and nasal flow pressure sensor), one pharyngeal sound lead (piezo vibration sensor) and two respiratory effort leads (thoracic and abdominal piezo crystal transducers) were included. Furthermore, one oxymeter lead (oxygen saturation level and pulse from a finger probe), two electrocardiography leads and one body position lead were included. Data were downloaded to the Somnologica reviewing analysis software (Version 2.0; Flaga Inc., Iceland) and sleep was scored manually in 30-second epochs according to standard criteria[14]. The polysomnography was considered acceptable when there was at least four hours of sleep recorded and no registration had been lost for ≥ 20 minutes of the night. A total of six

polysomnography recordings had to be redone due to poor quality of the first recording. An apnea was defined as the complete cessation of nasal and oral airflow lasting 10 seconds or more. Hypopnea was defined as a 50% or more reduction in airflow amplitude compared to baseline, in combination with a reduction of 3 % or more in oxyhaemoglobin saturation, or an arousal. An apnea-hypopnea index, AHI, (the average number of apneas and hypopneas per hour of sleep) was calculated.

Blood sampling and anthropometric variables

In the morning following the polysomnography, the women returned fasting to the laboratory. Venous blood samples were taken for analyses of plasma glucose, serum insulin and hemoglobin A1c.

Anthropometric variables (height, weight, waist circumference and hip circumference) were measured by a research nurse. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2) and then categorized into three groups: < 20, 20 to < 25 and ≥ 25 kg/m^2. Waist circumference was measured midway between the lower rib margin and the anterior superior iliac spine, hip circumference was measured at the widest circumference over the great trochanters, and the waist-to-hip circumference ratio (WHR) was calculated. Blood pressure was measured in the right arm after 15 minutes rest in a supine position.

Questionnaires

Prior to the polysomnography, the women filled in questionnaires, including questions on somatic disease, medication and questions on snoring, daytime sleepiness, physical activity, tobacco use and alcohol consumption.

The participants' physical activity was analyzed by four questions adopted from a questionnaire used in a large population-based study on the correlation of physical activity and mortality in women[15]. The women were asked to respond on a scale from 1 to 4, where 1= spending most leisure time at sedentary activities, 2= exercising at least four hours a week (walking, biking back and forth to work, etc.), 3= at least three hours of keep-fit exercises per week and 4= hard exercise several times a week. This gave three categories of physical activity: low activity (score 1), medium activity (score 2) and high activity (scores 3-4).

Six questions assessed smoking habits[16]. Based on the participants' responses they were categorized as 'current smokers' or 'non-smokers' (i.e. never smoked or had quit smoking at least 6 months before answering the questionnaire).

To investigate alcohol consumption the women were asked to state how many milliliters of different kinds of alcoholic beverages they drank per week. From this information the total amount of alcohol in grams per week was calculated using the formula: ((volume percentage alcohol (%) x total volume (ml))/100) x 0.7894 where 0.7894 is the density of the alcohol in grams/liter.

Oral Glucose Tolerance Test (OGTT)

Within approximately one month after the polysomnography (mean latency period 36 days), the women underwent an OGTT. Exclusion criteria for performing the OGTT were stating diabetes mellitus or medication for diabetes mellitus in the questionnaires. In addition, women having a fasting plasma glucose level ≥7.0 mmol/l at the time of the OGTT or women who refused to participate in the OGTT were excluded. The OGTT was performed in 358 of the women (Figure 1). The test was conducted by administration of 75g of glucose and venous

blood samples of plasma glucose and serum insulin were taken at 0, 30, 60, 90 and 120 minutes. Type 2 diabetes mellitus was defined according to WHO criteria as fasting plasma glucose ≥ 7.0 mmol/l or 2-h post glucose load ≥ 11.1 mmol/l. Impaired fasting glucose (IFG) was defined as having a fasting plasma glucose 6.1-7.0 mmol/l with 2-h post glucose load < 7.8 mmol/l[17]. Impaired glucose tolerance (IGT) was defined as fasting plasma glucose <7.0 mmol/l with 2-h post glucose load 7.8-11.1 mmol/l[17]. Impaired glucose metabolism was defined as stating type 2 diabetes mellitus in the questionnaires or having impaired fasting glucose, impaired glucose tolerance or type 2 diabetes mellitus according to the WHO criteria[17]. Insulin sensitivity was calculated as an index (insulin sensitivity index; ISI) based on fasting plasma glucose (FPG), fasting plasma insulin (FPI), mean OGTT glucose concentration and mean OGTT insulin concentration. The formula for ISI was 10,000/ ((FPG x FPI x Mean OGTT glucose concentration x 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[18].

Statistical analyses

Statistical analyses were performed using Stata 9.0 (Stata Corporation, College Station, TX, USA). Univariate analyses were conducted using the unpaired t-test or the chi-squared test to compare baseline data between groups. Associations between variables of OSA and glucose metabolism were analyzed using multiple regression analysis. As there was a close relationship between BMI and WHR ($r=0.34$; $p<0.0001$) only WHR was used in the multiple regression analysis. Results from the regression analysis are presented as β-values with 95% confidence intervals (CI). Furthermore, interaction analyses were conducted to detect significant differences in associations between OSA and insulin sensitivity in older (≥50 years) and younger women (<50 years). To detect differences between women in different

AHI groups from the OGTT, ANOVA analysis were performed using results from the five measure points of the OGTT. A p-value <0.05 was considered indicating a significant difference.

The study was approved by the Ethics Committee of the Medical Faculty at Uppsala University and all participants in the study gave their informed consent.

RESULTS

Table 1 shows the characteristics of the women with different levels of AHI. Women with an AHI of five or higher (i.e. women with OSA) had significantly higher mean fasting plasma glucose and mean fasting serum insulin compared with women with AHI<5. In addition, the insulin sensitivity index (ISI) was significantly lower in women with OSA than in women without and the women with OSA were also generally older, more overweight and more hypertensive. There was no significant difference in total sleep time between the groups of women; however, women with an AHI of 15 or higher had less REM sleep compared with women without OSA. Furthermore, the women in the highest AHI group showed significantly lower percentage of Stage 3 and 4 sleep compared with the women without OSA (Table 1).

The results from the OGTT are depicted in Figure 2a and Figure 2b. There were significant differences between the plasma glucose curve for women in different AHI groups throughout the OGTT, showing a dose-response relationship between AHI and plasma glucose. Furthermore, there was an inverse relationship between AHI and disappearance of plasma glucose. In addition, a dose-response relationship was seen between AHI and serum insulin thoughout the insulin curve (Figure 2b). Results from the OGTT were also analyzed in

women with BMI <27 kg/m^2 (population mean) but these results did not differ from those of the whole group (data not shown).

When calculating ISI in this population of women the number of women is 352. This is because in order to calculate ISI there needs to be no missing values on any of the samples throughout the OGTT. For six of the women who underwent the OGTT there were one missing value and therefore the ISI could not be calculated, making n=352. There was a gradual decrease in ISI with increasing AHI, i.e. women with AHI <5 evidenced an ISI of 8.3 (±3.8), whereas women with AHI ≥30 had an ISI of 6.2 (±4.0) (p for trend<0.0001, Figure 3). Furthermore, the prevalence of impaired glucose metabolism increased with AHI from 9.0% of the women with AHI <5 to 42.9% in women with AHI ≥30 (p for trend<0.0001; Figure 3).

Multivariate analysis

Multiple linear regression analysis was performed to assess the relationship between variables of obstructive sleep apnea and insulin sensitivity (Table 2). When controlling for the confounders age, waist-to-hip ratio, level of physical activity, smoking, and alcohol consumption a low nocturnal minimal saturation was significantly correlated to a decreased ISI. Moreover, low minimal saturation during the night was associated with higher plasma glucose and serum insulin concentrations at the end of the OGTT (2h). AHI was independently associated with fasting serum insulin concentration and increased concentrations of 2h-serum insulin at the OGTT. The percentage of time during the night with saturation <90 % was independently associated with fasting serum insulin levels, whereas the association with the ISI did not reach statistical significance. However, in women ≥50 years

(n=236) there was a significant association between percentage of night with saturation <90% and ISI (Table 3).

DISCUSSION

The main result of this study is that there is an association between OSA and insulin sensitivity in a population-based sample of women. This association is independent of age, waist-hip-ratio, level of physical activity, smoking, and alcohol consumption. Although the relationship between OSA and insulin sensitivity can partly be explained by shared risk factors, AHI was found independently associated with increased fasting serum insulin. In addition, low nocturnal minimal saturation was independently associated with decreased insulin sensitivity. Furthermore, AHI and measurements of hypoxia were independently associated with the late serum insulin response two hours after ingestion of 75g of glucose.

The dose-response relationship between AHI level and plasma glucose and serum insulin concentrations indicates that OSA may, as it worsens and AHI increases, gradually affect glucose metabolism and impair insulin sensitivity. A similar dose-response relationship has recently been reported in patients with obstructive sleep apnea syndrome[19, 20]. Independent associations between OSA and measures of glucose metabolism has also been reported in a population-based study of men[21] and in males with obstructive sleep apnea syndrome[12]. The negative impact of sleep-disordered breathing on glucose metabolism is further supported in a prospective study by the observation that snorers have an increased risk of developing diabetes[7]. Using either doctor's diagnosis or blood sampling results for diagnosis of diabetes, longitudinal data from the Wisconsin Sleep Cohort show that diabetes is more

prevalent in sleep disordered breathing and that this association is independent of other risk factors[22].

Subjects with OSA often exhibit coexisting risk factors (i.e. central obesity, dyslipidemia, hyperglycemia and hypertension) for cardiovascular disease and diabetes. In the present study, however, AHI and measurements of hypoxia were associated with changes in glucose metabolism, independent of age, central obesity, level of physical activity, smoking and alcohol consumption. These findings indicate that OSA decreases insulin sensitivity and may contribute to an increased risk of developing diabetes independently of central obesity. In addition, low minimal saturation was independently associated with a low ISI, suggesting that the negative influence of sleep disordered breathing on insulin sensitivity may be mediated though hypoxic pathways. Further, in several studies AHI and hypoxia have been related to glucose dysregulation and insulin resistance[11, 20, 23]. The present study also showed that in older women the association between hypoxia and insulin sensitivity was stronger, a result indicating that age may increase the sensitivity to hypoxia.

OSA can affect glucose metabolism and insulin sensitivity negatively through several pathways. First, lack of sleep influences metabolic and endocrine function with alterations of glucose and insulin profiles as a result, which decreases glucose tolerance[24]. Sleep loss has also been suggested to increase levels of cortisol through increased activity in the hypothalamic-pituitary-adrenal axis[25], a mechanism that can contribute to hyperglycemia. Second, the intermittent hypoxemia and reoxygenation accompanying obstructive apneas may trigger the formation of inflammatory cytokines[26] which promotes peripheral insulin resistance[27]. Vgontzas *et al* (2000) found higher levels of the inflammatory cytokines tumor necrosis factor alpha and interleukin-6 in patients with obstructive sleep apnea syndrome

compared with weight-matched controls without obstructive sleep apnea syndrome[28]. In addition, the deoxygenation and reoxygenation cycles in OSA provide an environment with increased oxidative stress[26, 29], which in combination with hyperglycemia may promote the formation of advanced glycation endproducts[30]. Advanced glycation endproducts are implicated in the progression of micro- and macrovascular complications of diabetes[31]. Finally, arousals accompanying the obstructive apnea increase nocturnal sympathetic activity and increased urinary and plasma catecholamines are displayed in OSA patients[32]. Sympathetic hyperactivity may also in turn negatively affect glucose homeostasis by enhancing hepatic glucose production and inducing skeletal muscle insulin resistance.

Effectively treating obstructive apneas, which reduces sleep loss, hypoxia and sympathetic hyperactivity in women with OSA may promote increased insulin sensitivity and reduce the risk of diabetes mellitus. Some studies show improved insulin sensitivity when patients with both diabetes and obstructive sleep apnea syndrome are treated with continuous positive airway pressure[2, 3, 10]. However, two recent studies have not shown improvement in insulin sensitivity with CPAP[5, 6]. In both these studies, the majority or all of the subjects were obese which may have had an impact on the outcome. In the earlier study by Harsch and co-workers[2] the improvement in insulin sensitivity by CPAP was smaller in the obese than in the non-obese patients. The authors suggested that insulin sensitivity in obese individuals is mainly determined by obesity and to a smaller extent by sleep apnea[2].

This study was conducted in a large population-based sample of women in which relevant objective data on OSA and glucose metabolism were collected. However, there are considerations when interpreting our results. The use of the ISI as a surrogate from the OGTT instead of the gold standard euglycemic insulin clamp when assessing insulin sensitivity may

be a less precise measure of insulin sensitivity. Nevertheless, the ISI used in the present study has been shown to provide a good estimate ($r=0.73$, $p<0.0001$) of whole-body insulin sensitivity when compared with the euglycemic insulin clamp[18].

In summary, in a population-based sample of women several features of OSA displayed independent associations with decreased insulin sensitivity. This indicates that decreased insulin sensitivity should be considered when treating patients with OSA.

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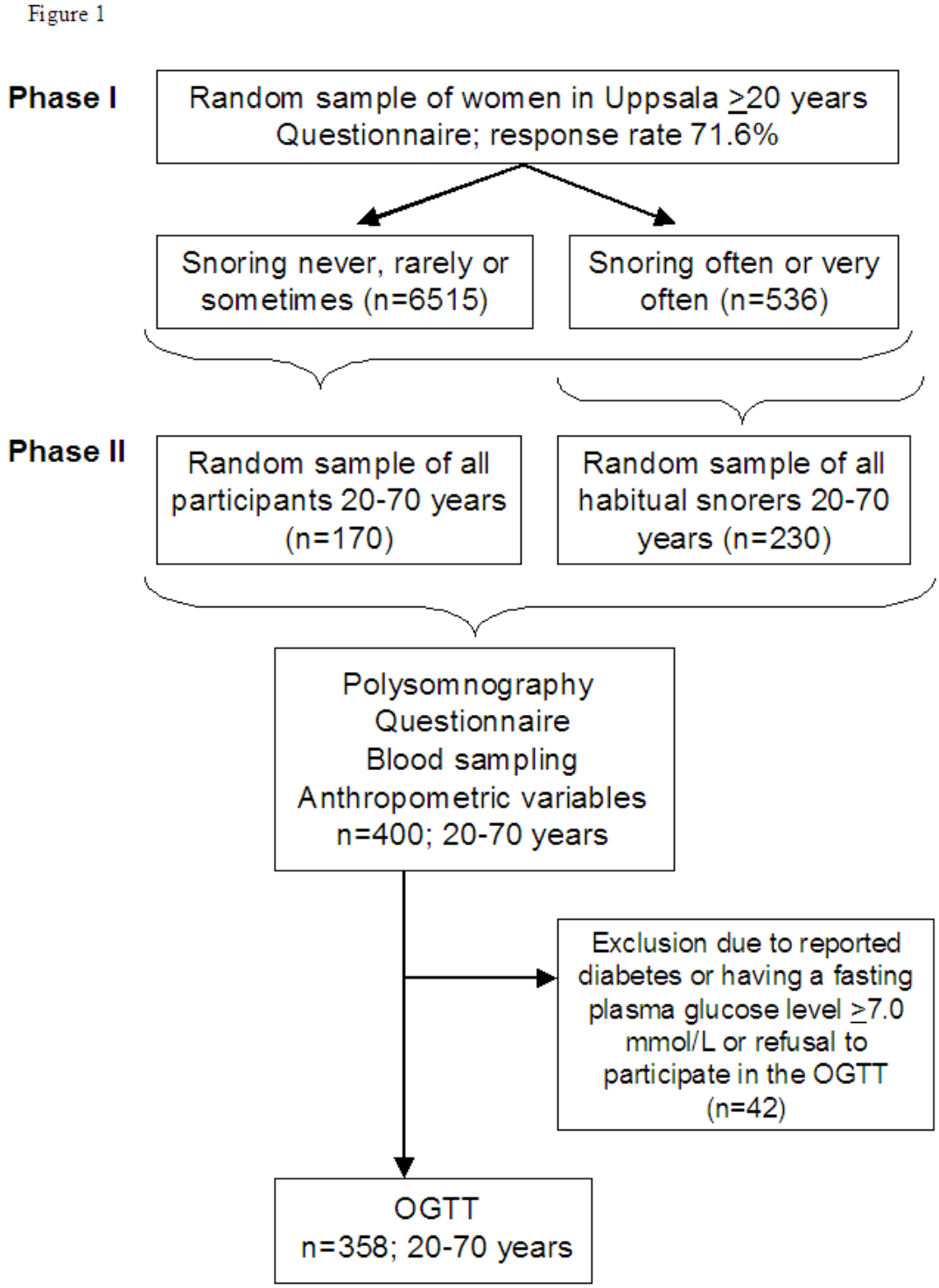
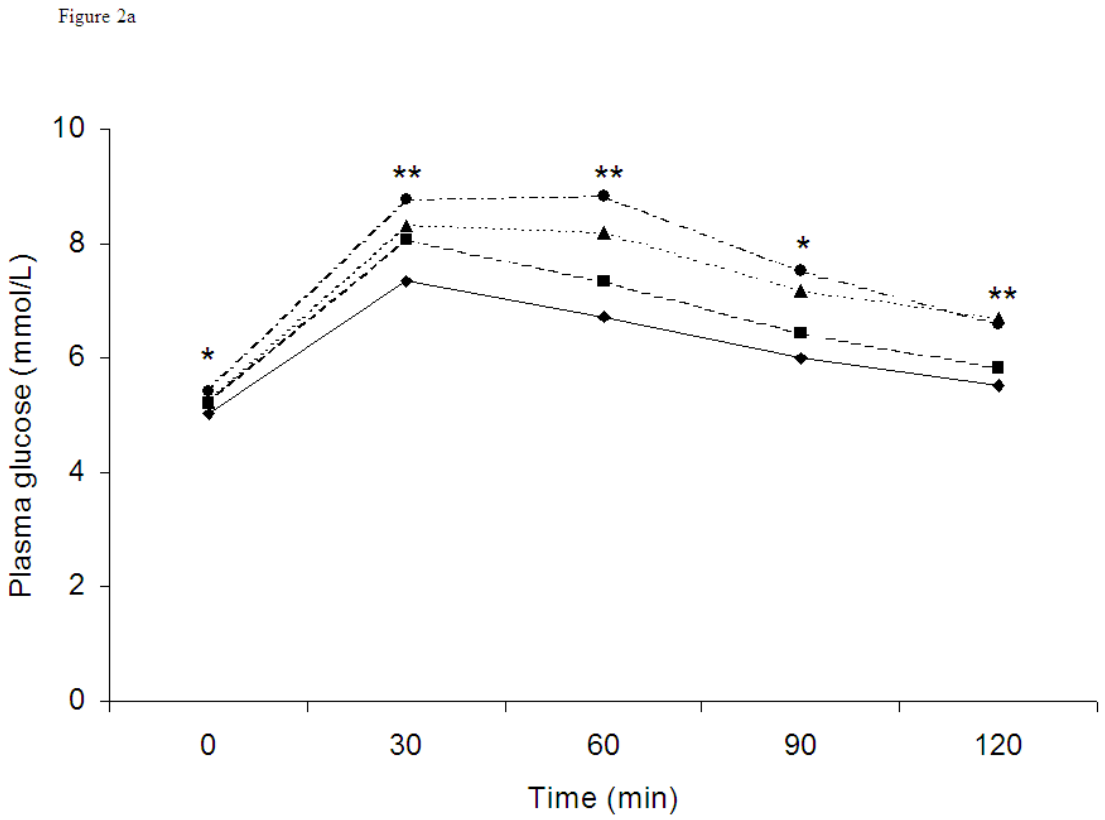
LEGENDS

Figure 1.



Flow chart of the study design.

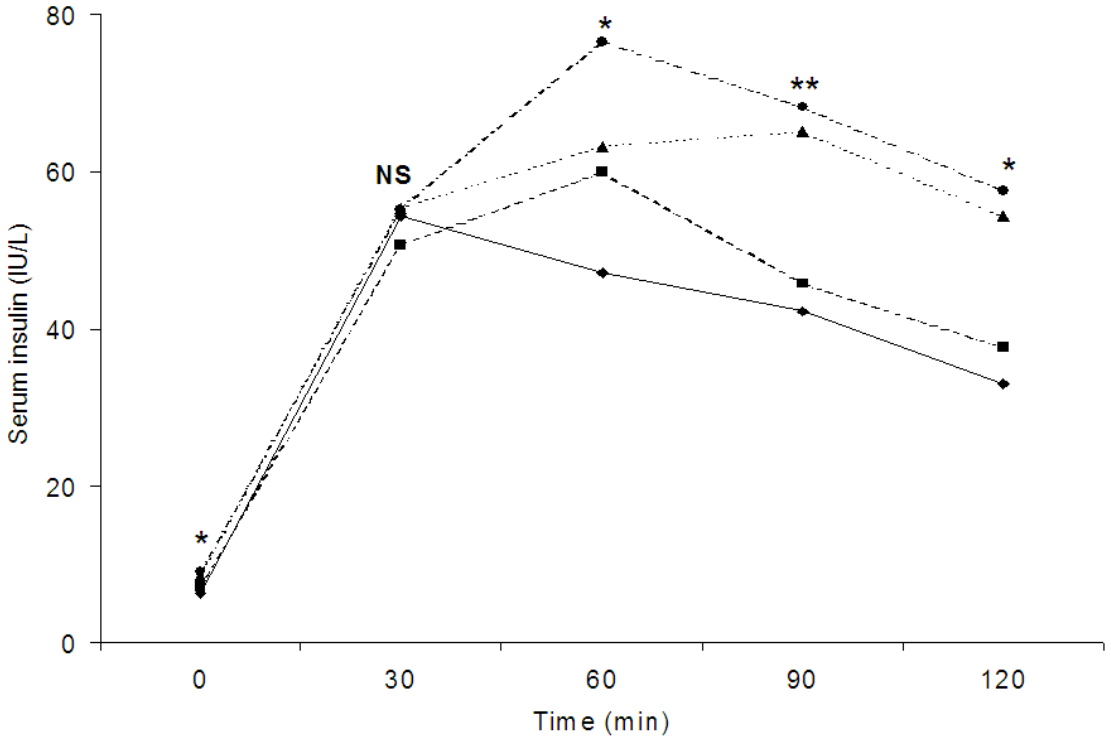
Figure 2a.



Plasma glucose concentrations during the OGTT in women with different AHI. P-values are calculated for differences between AHI groups at the five points of measurement (0, 30, 60, 90 and 120 minutes) in the OGTT using ANOVA; * p between groups <0.01; ** p between groups <0.0001. Filled lines show values for women with AHI <5 (n=120), dashed lines for AHI 5-<15 (n=115), dotted lines for AHI 15-<30 (n=88) and dashed with dots for AHI ≥30 (n=35).

Figure 2b.

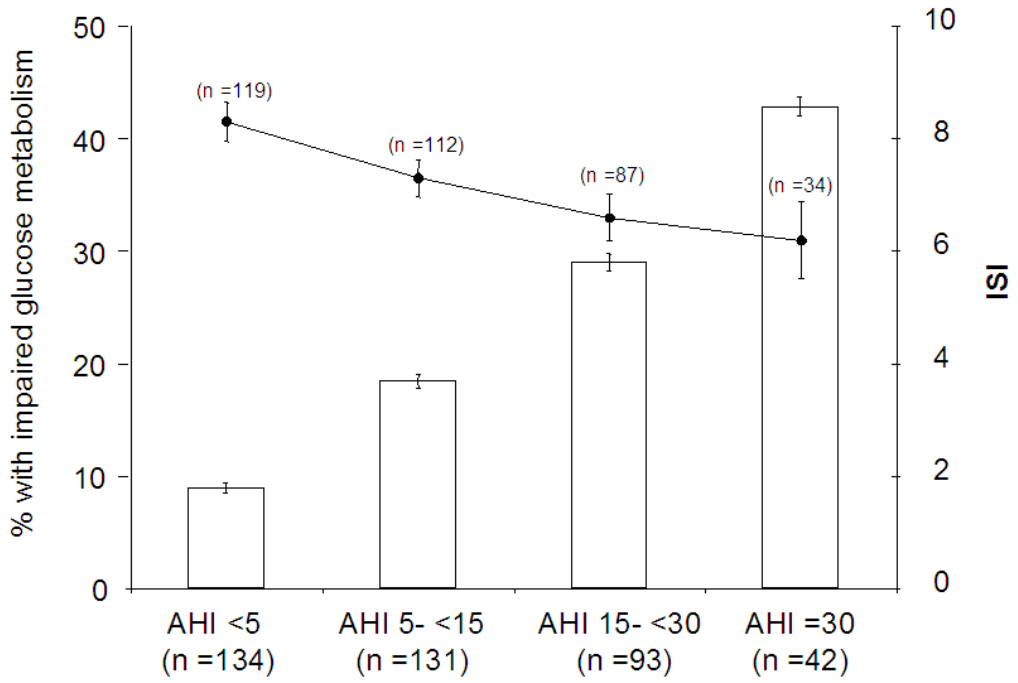
Figure 2b



Serum insulin concentrations during the OGTT in women with different AHI. P-values are calculated for differences between AHI groups at the five points of measurement (0, 30, 60, 90 and 120 minutes) in the OGTT using ANOVA; * p between groups <0.01; ** p between groups <0.0001. Filled lines show values for women with AHI <5 (n=120), dashed lines for AHI 5-<15 (n=115), dotted lines for AHI 15-<30 (n=88) and dashed with dots for AHI ≥30 (n=35).

Figure 3.

Figure 3



Prevalence of impaired glucose metabolism and mean insulin sensitivity index in women of different AHI groups. Filled bars show the prevalence of impaired glucose metabolism in percent with 95% confidence intervals. The line shows mean ISI ± SE. When calculating ISI, no missing values on any of the samples throughout the OGTT are allowed. Therefore, the number of women in different AHI groups is lower for ISI than for impaired glucose metabolism, and is put in brackets in the figure.

Table 1.

Characteristics of women in different OSA groups. Results are presented as mean ± SD or n (%); p values are calculated using women with AHI<5 as control.

	Women with AHI <5 (n= 134)	**Women with AHI1 5-15** (n= 131)	**p-value**	**Women with AHI1 15-30** (n=93)	**p-value**	**Women with AHI1 ≥30** (n=42)	**p-value**
ODI	0.69 ±0.80	3.0 ±2.7	<0.0001	10.6 ±4.4	<0.0001	30.1 ±21.1	<0.0001
Mean saturation	96.0 ±1.60	95.3 ±1.7	0.0006	94.8 ±1.4	<0.0001	93.9 ±1.8	<0.0001
Minimal saturation	91.1 ±4.8	88.0 ±5.4	<0.0001	85.2 ±5.1	<0.0001	81.1 ±6.5	<0.0001
Age (yr.)	43.5 ±11.4	50.9 ±9.9	<0.0001	54.8 ±9.6	<0.0001	58.0 ±6.3	<0.0001
Total sleep time (min)	394.9 ±72.2	386.8 ±72.2	0.37	377.5 ±64.0	0.06	373.3 ±71.1	0.09
Sleep latency (min)	22.9 ±27.8	21.8 ±21.8	0.70	24.7 ±27.3	0.63	22.6 ±22.3	0.94
Stage 3+4 sleep (%)	10.6 ±5.9	9.3 ±5.4	0.07	9.6 ±5.8	0.21	7.7 ±5.9	0.006
REM sleep (%)	19.0 ±6.0	18.8 ±8.22	0.81	17.2 ±6.1	0.03	14.6 ±7.1	0.0001
BMI (kg/m2)	24.7 ±3.7	26.5 ±4.8	0.0005	27.8 ±5.1	<0.0001	30.8 ±5.8	<0.0001
WHR	0.83 ±0.08	0.85 ±0.06	0.04	0.87 ±0.06	0.0002	0.90 ±0.8	<0.0001
Plasma glucose (mmol/L)	5.2 ±0.83	5.5 ±1.2	0.02	5.5 ±0.80	0.03	6.1 ±1.7	<0.0001
Serum insulin (mU/L)	6.4 ±3.5	7.5 ±6.6	0.09	8.8 ±6.3	0.0004	10.1 ±6.7	<0.0001
Insulin sensitivity index, ISI (mg/dl)	8.3 ±3.8	7.3 ±3.6	0.049	6.6 ±3.9	0.001	6.2 ±4.0	0.004
Impaired glucose metabolism*	12 (9.0)	24 (18.3)	0.03	28 (30.1)	<0.0001	18 (42.9)	<0.0001
Hypertension†	36 (26.9)	68 (51.9)	<0.0001	54 (58.1)	<0.0001	31 (73.8)	<0.0001
Smoker	29 (21.6)	23 (17.8)	0.44	21 (23.1)	0.80	11 (28.2)	0.44
Physical activity			0.50		0.17		0.16
- High	29 (21.8)	22 (17.1)		11 (12.2)		4 (10.0)	
- Medium	90 (67.7)	89 (69.0)		70 (77.8)		29 (72.5)	
- Low	14 (10.5)	18 (14.0)		9 (10.0)		7 (17.5)	

Alcohol (grams/week)	54.1 ±66.1	56.3 ±52.2	0.77	54.2 ±52.6	0.85	57.1 ±62.9	0.73

* Having impaired fasting glucose or impaired glucose tolerance or type 2 diabetes mellitus
† Systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥90 mmHg or known hypertension or being medicated for hypertension.

Table 2.

Associations between variables of OSA and glucose metabolism obtained at the OGTT.

	Fasting plasma glucose (mmol/L)	Fasting serum insulin (IU/L)	Plasma glucose at 120 min (mmol/L)	Serum insulin at 120 min (IU/L)	ISI*
AHI[1]	0.13 (-0.07, 0.09)	0.56 (0.14, 0.99)	0.024 (-0.12, 0.17)	3.38 (0.28, 6.47)	-0.12 (-0.41, 0.17)
ODI[1]	-0.012 (-0.10, 0.07)	0.37 (-0.08, 0.83)	-0.007 (-0.16, 0.15)	1.81 (-1.43, 5.06)	-0.18 (-0.48, 0.12)
Minimal saturation	-0.013 (-0.03, 0.005)	-0.038 (-0.14, 0.06)	-0.046 (-0.079, -0.013)	-0.77 (-1.48, -0.07)	0.07 (0.004, 0.14)
% of the night with saturation <90%	0.014 (-0.004, 0.03)	0.10 (0.001, 0.20)	0.026 (-0.13, 0.07)	0.098 (-0.74, 0.94)	-0.04 (-0.12, 0.04)

Results are presented as β-values with 95% CI from multiple regression analysis adjusting for age, waist-to-hip ratio, level of activity, smoking and alcohol consumption.
* Insulin sensitivity index
[1] Results are calculated for an increase of 10 units.

Table 3.

Associations between variables of OSA and insulin sensitivity index (ISI) in women of different age groups.

	ISI < 50 years (n = 140)	**ISI ≥ 50 years (n = 204)**	**$p_{interaction}$**
AHI[1]	-0.29 (-1.01, 29.5)	-0.09 (-0.40, 0.21)	0.977
ODI[1]	-0.41 (-1.26, 0.44)	-0.16 (-0.47, 0.16)	0.882
Minimal saturation	-0.02 (-0.15, 0.12)	0.11 (0.04, 0.19)	0.058
% of the night with saturation <90%	0.13 (-0.06, 0.33)	-0.08 (-0.17, -0.004)	0.012

Results are presented as β-values with 95%CI from multiple regression analysis adjusting for age, waist-to-hip ratio, level of activity, smoking and alcohol consumption.
[1] Results are calculated for an increase of 10 units.