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Metabolic Syndrome, Insulin Resistance and Sleepiness in Real-Life Obstructive Sleep Apnea

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Running head: Sleep apnea, sleepiness and metabolic syndrome

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Abstract (198 words, 200 max)

Questions of the study: The Metabolic Syndrome shows a variable prevalence in obstructive sleep apnea (OSA), and its association with insulin resistance or excessive daytime sleepiness in OSA is unclear. This study assessed in consecutive patients with newly diagnosed OSA: 1) the prevalence of Metabolic Syndrome, and 2) its association with insulin resistance and daytime sleepiness.

Patients and Methods: Metabolic Syndrome (NCEP-ATP III criteria), insulin resistance (Homeostatic Model Assessment Index, n= 288) and daytime sleepiness (Epworth Sleepiness Scale) were assessed in 529 OSA patients.

Results: Prevalence of Metabolic Syndrome was 51.2%, and increased with OSA severity. Each Metabolic Syndrome component correlated with AHI, but only blood pressure retained significance after correction for confounders. Both obesity and OSA contributed to metabolic abnormalities, with different gender-related patterns, since diagnosis of MetS was significantly associated with neck circumference, age BMI, and lowest SaO_2 in men, and with age and arousal index in women. The number of MetS components increased with HOMA Index ($p<0.0001$). Prevalence of sleepiness was the same in patients with and without Metabolic Syndrome.

Conclusions: The Metabolic Syndrome occurs in about half of "real life" OSA patients irrespective of daytime sleepiness, and is a reliable marker of insulin resistance.

List of abbreviations

MetS: Metabolic Syndrome

OSA: Obstructive Sleep Apnea

EDS: Excessive Daytime Sleepiness

IR: Insulin Resistance

AHI: Apnea-Hypopnea Index

SaO2: Arterial Oxyhemoglobin Saturation

ArI: Arousal Index

WC: Waist Circumference

TG: Triglycerides

FBG: Fasting Blood Glucose

HDL-C: High Density-Lipoprotein Cholesterol

HT: Hypertension

HOMA: Homeostatic Model Assessment

NCEP-ATP III: National Cholesterol Education Program - Adult Treatment Panel III

ESS: Epworth Sleepiness Scale

CPAP: Continuous Positive Airway Pressure

BMI: Body Mass Index

Introduction

Obstructive sleep apnea (OSA) is often associated with obesity, hypertension, and other cardiovascular risk factors (1), and untreated patients with severe OSA show an increased risk for cardiovascular morbidity and mortality (2, 3). However, since OSA and obesity frequently coexist, their respective role in increased cardiovascular risk is still debated.

Several studies have shown that insulin resistance (IR) occurs in OSA patients and directly correlates with OSA severity (see ref. 4 for review). Besides obesity, OSA may play an independent role in the pathogenesis of IR, since intermittent hypoxia was shown to cause IR in healthy humans (5). However, the available data are somewhat controversial, since the association of OSA and IR was mostly accounted for by obesity in at least four studies (6-9), and short-term treatment of OSA with continuous positive airway pressure (CPAP) failed to improve metabolic abnormalities (4).

The Metabolic Syndrome (MetS) is a cluster of risk factors associated with IR, increased risk for type 2 diabetes (10), and increased overall and cardiovascular mortality (11). Although its value in cardiovascular risk prediction is debated, the concept of MetS has gained popularity and improved clinicians' awareness of metabolic problems in obese subjects (12). According to the latest NCEP-ATP III definition (13), the MetS is diagnosed when at least three of the following conditions occur: increased waist circumference, as a marker of central obesity; increased blood pressure; fasting hyperglycemia; increased serum triglyceride and decreased high-density lipoprotein-cholesterol concentrations.

Prevalence of the MetS in OSA patients according to the NCEP-ATP III definition was found to range between 23 and 87% (14-19). Most studies included small

number of patients and did not assess IR in conjunction with MetS. One case-control study (7) and a cross-sectional population study (20) suggested that MetS, but not IR, was associated with OSA. Surprisingly, the value of MetS in predicting IR has not been specifically tested in OSA patients. Therefore, our first aim was to assess the prevalence of the MetS in a large sample of consecutive OSA patients at diagnosis and to compute relationships between sleep characteristics, insulin resistance and metabolic abnormalities.

Excessive daytime sleepiness (EDS) is a major symptom of OSA. EDS in OSA patients was reported to be associated with hypertension (21) altered autonomic modulation (22), and type 2 diabetes (23). EDS was among the factors significantly associated with OSA and MetS in the recent study by Agrawal and associates (18). Two case-control studies have found that EDS predicted IR in OSA patients independent of obesity (24, 25); only sleepy patients showed improved insulin sensitivity after CPAP treatment for 3 months (24). Conversely, other studies have found similar degree of subjective sleepiness in MetS patients with or without OSA (26). Therefore, the second aim of the current investigation was to assess the characteristics of OSA patients reporting daytime sleepiness and whether EDS is associated with MetS in a large series of OSA patients.

Methods

Patients

Consecutive patients referred to the Sleep Laboratory, Hospital Son Dureta, Palma de Mallorca, Spain in the years 2005-2007 were studied (n=535). Inclusion criteria were: age >18 years, diagnosis of OSA, and wish to participate to the study. No

eligible patient refused to participate. Six patients were excluded due to missing data, reducing the sample to 529 patients. The study protocol was approved by the local Institutional Review Board (approval number IB741/09PI), and all participants gave their informed written consent.

Sleep study

OSA was diagnosed by full polysomnography (E-Series Compumedics, Abbotsford, Australia) that included recording of oronasal flow, thoraco-abdominal movements, electrocardiogram, submental and pretibial electromyography, electrooculogram, electroencephalogram and pulse oximetry as previously described (22). Apnea was defined by absence of airflow lasting 10 s or longer. Hypopnea was defined as any airflow reduction lasting 10 s or longer associated with either oxygen desaturation ≥ 4%, or arousal and oxygen desaturation ≥ 3%. The apnea-hypopnea index (AHI) and the arousal index (ArI) were defined as the number of apneas and hypopneas, and of arousals, respectively, per hour of sleep. OSA was diagnosed if AHI was ≥10 events/h. Subjective daytime sleepiness (EDS), quantified by the Epworth Sleepiness Scale (ESS), was defined as an ESS score ≥10.

Metabolic Syndrome

As a general measure of obesity, BMI was defined as weight/height^2 (kg/m^2). Neck and waist circumferences (in cm) were also measured. The Metabolic Syndrome was diagnosed based on the presence of 3 or more of the following factors: waist circumference ≥ 80 cm in women and ≥ 94 cm in men (all patients were Caucasian); serum triglycerides ≥150 mg/dL, or lipid-lowering treatment; high density lipoprotein

(HDL)-Cholesterol <40 mg/dL in men, <50 mg/dL in women, or lipid-lowering treatment; increased blood pressure (see below), or anti-hypertensive treatment; and fasting blood glucose >100 mg/dL or antidiabetic treatment (13).

Office blood pressure was measured by a standard mercury sphygmomanometer while the subject was quietly seated after at least 5 min of rest. Increased blood pressure was recorded if systolic blood pressure (SBP) was >130 mm Hg, or diastolic pressure (DBP) was >85 mm Hg, or the patient was on anti-hypertensive treatment.

Fasting venous blood samples were obtained in the morning after polysomnography. Glucose, triglycerides, total cholesterol and HDL-cholesterol were determined by standard enzymatic methods on a Hitachi Modular analyser (Roche Diagnostics, Indianapolis, USA). In 288 patients without previously known diabetes, plasma insulin concentration was measured by chemiluminescent assays on a Immulite 2000 analyser (Siemens Medical Solutions Diagnostics, New York, USA). Insulin resistance was calculated using the Homeostasis Model Assessment (HOMA) index (27).

Statistical analysis

Data are presented as mean ± standard deviation (SD); categorical data are shown as percentage of positive patients.

Student t-test (numerical variables), or U-Mann Withney non-parametric test (not normally distributed variables), were used to compare: a) patient characteristics according to gender; b) patients without any MetS components vs. all other patients; c) patients without and with a diagnosis of MetS, and d) patients without and with EDS. Frequencies were compared by the Chi-square test for categorical variables (exact

Fisher test with observed frequencies < 5). Due to non-normal distribution, HOMA index and serum trygliceride values were analyzed after logarithmic transformation.

Trends were analyzed by the Spearman rank test, or the Kendall Tau-c for categorical variables. Multiple linear regression was used to assess the relationship between AHI, Arousal Index, and SaO_2 as independent variables and each MetS component as dependent variable.

The multivariate logistic regression model was used to assess determinants of MetS and EDS. To this aim, we used anthropometric and sleep variables together with the variables showing a $p<0.20$ in bivariate analysis. Variables were selected by using a stepwise approach. A p value <0.05 was considered significant. The SPSS v. 17 software was used for all analyses.

Results

1. Metabolic Syndrome

Total sample and gender-specific characteristics are reported in Table 1. OSA patients were mostly male and obese. Women accounted for about a fifth of the total sample (n=105). Neck circumference and AHI were significantly higher in men than in women.Current smokers accounted for 29% of the subjects, while COPD or cardiovascular disease (coronary artery disease and heart failure) occurred in 6.6 and 5.9% of the subjects, respectively, without differences between genders (data not shown).

Overall prevalence of the MetS was 51.2%. The number of MetS components increased with OSA severity (Table 2 and Figure 1); mild, moderate and severe OSA patients showed significantly different distribution of MetS components, with mild patients being often free of any MetS component, and severe patients frequently showing 3-5 MetS components. Patients with 1 or 2 MetS components included all degrees of OSA severity without any specific distribution pattern (Figure 1).

The distribution and prevalence of MetS components in the sample are shown Figure 2. The most common combinations of MetS components included increased waist circumference, hypertension, and abnormal fasting blood glucose (Table A, online repository).

Some patients (n=55) showed no MetS component. Compared to patients with 1 or more MetS components, they were nonobese, had mild-moderate OSA, were significantly younger (Table B, online repository), and included more active smokers (data not shown).

Markers of OSA severity (AHI, mean SaO_2, Table 4) showed significant unadjusted linear relationships with each component of the MetS. Most of the significance was lost for AHI after adjustments for age, BMI, smoking, and gender except for systolic and diastolic blood pressure. Mean SaO_2 remained significantly associated with waist circumference and diastolic blood pressure after adjustments. Arousal index and lowest SaO_2 were also analyzed, with results similar to those obtained for AHI and mean SaO_2, respectively (Table C, online repository)

2. **Insulin Resistance**

Insulin resistance, estimated by the HOMA index in 288 patients, increased with increasing number of MetS components (Spearman's rho: 0.455, $p<0.001$, Figure 3). The HOMA index correlated positively with AHI and Arousal Index, and negatively with lowest or mean SaO_2 in unadjusted bivariate analysis ($p<0.0001$, data not shown). All such relationships became nonsignificant after adjustment for BMI and were unaffected by gender (data not shown).

3. Sleepiness

Prevalence of the MetS, or of each of its components, was similar in patients with and without EDS (Figure 2). The relationship between HOMA index and number of MetS components was comparable in OSA patients with (0.466, $p<0.001$) and without EDS (0.426, $p<0.001$) (Figure 3). ESS and HOMA index did not show any significant relationship. Patients free from any MetS component showed similar EDS than the rest of the sample (Table B, online repository). No difference was found in EDS between patients without and with a MetS diagnosis (Table 3). Patients with EDS

were younger, showed a slightly higher waist circumference, worse polysomnographic variables, but similar blood pressure or other metabolic variables compared with non-sleepy patients (Table 3).

3. Logistic regression analysis

To assess the factors associated with the MetS in whole sample, the following variables were entered in the model: EDS, BMI, neck circumference, gender, age, AHI, Arousal Index, Apnea Index, lowest and mean nocturnal SaO_2. The MetS in OSA was significantly associated with: gender (OR: 1.033, CI 1.013-1.054, p=0.001), neck circumference (OR: 1.174, CI 1.057-1.304, p=0.003), arousal index (OR: 1.027, CI 1.005-1.048, p=0.014), BMI (OR: 1.083, CI 1.010-1.162, p=0.03), lowest nocturnal SaO_2 (OR: 0.953, CI 0.910-0.997, p=0.036), Age showed a strong trend (OR: 1.033, CI 0.998- 5.3, p=0.05), while EDS did not contribute significantly (OR: 1.220, CI 0.780-1.907, p= NS).

To better explore gender-related differences, the analysis was repeated separately in men and women. In men, the MetS was significantly associated with: neck circumference, age, BMI and lowest nocturnal SaO_2, the regression accounting for 42.3% of the variability. In women, arousal index and age explained 52.4% of MetS variability, and lowest nocturnal SaO_2 showed a strong trend for association with MetS (p=0.053).

Factors associated with EDS in the entire sample were also analyzed. Age (OR: 0.979, CI 0.963-0.995, p=0.01) and mean nocturnal SaO_2 (OR: 0.917, CI 0.869-0.968, p=0.002) were negatively associated with EDS, and explained 20% of EDS variability.

Discussion

In a large "real life" sample of OSA patients at diagnosis, the MetS according to NCEP-ATP III criteria occurred in about half of the subjects, and severe OSA was significantly associated with a diagnosis of MetS, i.e. occurrence of 3 or more components of the syndrome. An increasing number of MetS components was associated with worsening insulin resistance; correlations between markers of OSA severity and the HOMA index became nonsignificant after adjusting for BMI, indicating a major role of obesity in the relationship between OSA and IR. Each of the MetS components showed crude linear relationships with markers OSA severity but after adjustment for confounders AHI remained significantly correlated only to blood pressure, and mean SaO_2 remained correlated only to waist circumference and diastolic blood pressure. Therefore, the MetS was associated with both obesity- and OSA-related variables. EDS resulted a poor clinical marker of metabolic abnormalities, and nocturnal intermittent hypoxia and age explained a small fraction of EDS variability.

Prevalence of the MetS

Clinical studies in OSA patients have reported variable prevalence of the MetS according to NCEP-ATP III criteria, with values ranging between 23% and 87% (14-19). The largest published series (819 Japanese patients) found prevalence of the MetS to be 49.5% in males and 32% in females (15). Our results are similar for male patients, but the prevalence rate of MetS in our female patients was higher, possibly due to more severe obesity in our sample.

Case-control studies reported variable prevalence rates of the MetS, or IR and MetS components (7, 28). Similar to the study by Kono and associates (28) increased waist circumference, hypertension and increased fasting blood glucose were the commonest MetS components. Instead, the study by Sasanabe and associates reported dyslipidemia as the third most frequent finding (15). Finally, population-based studies yielded a prevalence of MetS in OSA between 26 and 35% (29-31). A recent population study reported a 44% prevalence of MetS in women with AHI>15 (32).

Components of the MetS and insulin resistance

The MetS is considered as the clinical manifestation of IR (10, 13). Two studies, however, reported that IR may not be associated with MetS in OSA patients. In the Turkish population, OSA in men was associated with MetS but not with IR (20). A case-control study reported similar results (7). The linear increase of the HOMA Index with an increasing number of MetS components found in our study suggests that such number, known as the Metabolic Index, may be a clinically useful indicator of the metabolic load in OSA patients. When the data were stratified for OSA severity, occurrence of 1 or 2 components of the MetS showed similar frequencies in patients with mild, moderate or severe OSA, whereas a diagnosis of MetS (i.e. 3 or more components) was more frequent in severe OSA, and absence of any MetS component prevailed in mild OSA. These findings agree with those reported by Theorell-Haglöw and coworkers in a population-based study on women (32), indicating that the association between OSA and MetS is especially strong in patients with severe OSA.

The number of MetS components carries prognostic implications. Both all-cause and cardiovascular mortality increased with the number of MetS components (11),

hypertension being the most potent factor, followed by central obesity and hypertrygliceridemia. Other studies found increased risk only in patients with 3 or more MetS components (33), or reported that a diagnosis of MetS was not superior to the sum of individual risk factors in predicting cardiovascular mortality (34), severity of vascular lesions or progression of atherosclerosis (35). No longitudinal data are yet available on the prognostic significance of MetS components in OSA patients.

About 10% of our patients did not show any MetS component. This subset differed from the rest of the sample as they were younger, non-obese, and had mild OSA. It is possible that absence of metabolic derangements represents an early stage in the natural history of OSA, but longitudinal studies are necessary to test this hypothesis. Alternatively, these patients may represent a distinct, still incompletely characterized, clinical OSA phenotype. Interestingly, the metabolic effects of intermittent hypoxia were recently shown to be quite small in lean mice (36). If the same results were to be shown in humans with OSA, the patients without any MetS component may represent a low-risk subgroup, with obvious consequences regarding treatment. Some studies, however, found metabolic abnormalities in nonobese OSA patients, even though a diagnosis of MetS was not fulfilled (19, 28, 37). On the other hand, both morbidly obese patients (38) and patients with the MetS (26) showed worse metabolic variables associated with severe OSA compared to subjects without OSA.

Relationships between MetS, OSA and obesity

Our study found that age, lowest SaO_2, BMI, neck circumference and arousal index resulted significantly associated with MetS by multiple regression analysis, suggesting an independent role of OSA in addition to obesity. Neck circumference was found to

independently predict cardiovascular risk in a large population-based study (39), but prevalence of OSA was not assessed, indicating the need to further study the impact of fat distribution on the complex relationship between OSA, obesity and metabolism. Gender may also play a role, as suggested by the results obtained by separate analysis of men and women. In men, markers of central obesity and intermittent hypoxia were significantly associated with MetS, whereas in women only age and arousal index were significant factors, possibly suggesting a major role of sleep fragmentation in the female gender.

Sleepiness and MetS

Excessive daytime sleepiness has been proposed as a marker of OSA severity, especially for cardiovascular and metabolic outcomes (21-25). Two case-control studies reported that EDS in OSA was associated with IR, suggesting that it could be used clinically as a marker of cardiometabolic abnormalities. Other studies, however, did not confirm such findings (26, 40). In our study, EDS correlated negatively with age and mean nocturnal SaO_2, and did not affect the relationship between OSA and metabolic variables. The discrepancy between results of case-control studies and our "real life" study likely stems from the characteristics of the samples, since highly selected patients without comorbidities were examined in the studies by Barcelo' or Nena and coworkers. We acknowledge that the Epworth Sleepiness Scale does not assess sleepiness objectively, and lack of MSLT data is a major limitation of our study.

Conclusions

The MetS according to NCEP-ATPIII criteria occurs in about half of OSA patients at diagnosis, an additional 38.2% of patients showing 1-2 MetS components. The number of MetS components correlated with the HOMA Index in OSA patients, and can be used as a clinical marker of IR. EDS, instead, did not result to be a sensitive clinical marker of a detrimental metabolic profile in real-life OSA patients.

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Table 1. Antropometric and sleep characteristics of the sample.

	All patients (n=529)	**Men (n=424)**	**Women (n=105)**
Age, yrs	51.3 ± 12.8	50.9 ± 13.0	52.9 ± 12.0
Hypertension, % of subjects	35.2 %	36.6 %	29.5 %
Dyslipidemia, % of subjects	32.5 %	35 %	30.0 %
Diabetes mellitus, % of subjects	17.0 %	16.5%	19 %
Body Mass Index (BMI), kg/m^2	30.8 ± 6.0	30.6 ± 5.4	31.6 ± 7.9
Obesity (BMI ≥ 30 kg/m^2), % of subjects	49 %	48.3 %	51.4 %
Neck Circumference, cm	41.6 ± 4.1	42.7 ± 3.5	37.3 ± 3.8*
Apnea Hypopnea Index (AHI)	43.4 ± 27.6	44.8 ± 26.7	37.7 ± 30.7**
Arousal Index (ArI)	51.5 ± 23.2	52.4 ± 22.6	47.8 ± 25.3
Mean nocturnal oxygen saturation (SaO_2), %	92.3 ± 4.0	92.1 ± 4.0	93.0 ± 4.0
Lowest SaO_2, %	80.8 ± 9.3	80.5 ± 9.3	81.6 ± 9.4
Epworth Sleepinees Scale score (ESS)	9.7 ± 5.1	9.8 ± 5.0	9.5 ± 5.5
Daytime sleepiness (ESS>10), % of subjects	51.8 %	51.4 %	53.3 %
Diagnosis of Metabolic Syndrome, % of subjects	51.2 %	51.4 %	50.5 %
High blood pressure, % of subjects	54.6 %	55.4 %	51.4 %
High waist circumference, % of subjects	72 %	70.8 %	77.1 %
Low HDL-Cholesterol, % of subjects	26.8 %	26.7 %	27.6 %
High triglyceride level, % of subjects	45.9 %	47.6 %	39 %
High fasting blood glucose, % of subjects	49.9 %	50.7 %	46.7 %

Legend Table 1: Continuous data are expressed as mean ± SD. Nominal variables are shown as % of positive subjects. *$p<0.001$, **$p=0.02$ significant difference between genders by unpaired t-test or Chi square analysis.

Table 2. Progressive metabolic impairment is associated with increasing OSA severity, but not with increasing EDS

	No MetS Component (n= 55)	**1 MetS component (n=81)**	**2 MetS components (n=121)**	**3 MetS components (n=134)**	**4 MetS components (n=94)**	**5 MetS components (n=44)**	**Rho/tau**
Age, yrs	40.9 ± 13.1	46.6 ± 12.0	52.5 ± 12.5	52.9 ± 11.8	54.3 ± 11.5	55.9 ± 13.4	0.305*
Diabetes, % of subjects	0	0	10	20.5	36.4	47.7	0.338*
BMI, kg/m^2	24.5 ± 2.7	28.2 ± 4.6	29.7 ± 5.2	32.5 ± 5.5	34.2 ± 6.1	34.4 ± 5.6	0.548*
Obesity (BMI≥30), % of subjects	3.7 %	28.0 %	48.6 %	68.6 %	81 %	84.6 %	0.517*
Neck Circumference, cm	37.5 ± 3.2	39.6 ± 3.7	41.1 ± 3.3	42.3 ± 3.7	44.2 ± 4.1	43.8 ± 4.0	0.462*
Apnea Hypopnea Index (AHI)	22.9 ± 17.6	31.5 ± 20.8	36.8 ± 23.5	49.9 ± 26.8	56.2 ± 28.1	61.9 ± 31.2	0.428*
Arousal Index (ArI)	34.3 ± 16.9	41.6 ± 17.0	46.1 ± 20.7	56.2 ± 22.6	64.2 ± 23.5	65.0 ± 22.4	0.428*
Mean SaO_2 %	95.3 ± 2.0	94.1 ± 2.3	93.2 ± 2.8	91.5 ± 4.1	90.2 ± 4.6	90.2 ± 4.9	-0.466*
Lowest SaO_2 %	87.1 ± 5.7	84.6 ± 6.7	83.1 ± 7.2	78.2 ± 9.4	77.6 ± 9.8	74.3 ± 11.5	-0.419*
ESS score	9.9 ± 5.2	9.7 ± 5.3	9.0 ± 4.9	9.7 ± 5.1	10.5 ± 4.9	9.7 ± 5.6	0.036
Systolic Blood Pressure, mmHg	113.3 ± 8.5	121.7 ± 13.7	130.3 ± 16.9	135.0 ± 15.2	139.3 ± 17.7	144.1 ± 10.5	0.522*
Diastolic Blood Pressure, mmHg	68.0 ± 9.0	74.6 ± 9.4	79.6 ± 11.5	82.6 ± 12.3	85.2 ± 11.2	86.8 ± 10.7	0.429*
Waist circumference, cm	88.9 ± 9.3	99.8 ± 11.5	105.3 ± 11.1	112.4 ± 12.0	115.4 ±13.1	114.8 ±11.5	0.575*
HDL-Cholest, mg/dL	60.1 ± 13.6	57.1 ± 14.9	57.4 ± 22.7	51.3 ± 10.6	49.8 ± 22.3	41.6 ± 11.7	-0.363*
Triglycerides, mg/dL	85.6 ± 31.4	113.3 ± 58.0	129.8 ± 54.2	160.0 ± 74.3	205.5 ± 94.8	245.8 ± 132.1	0.598*
Fasting blood glucose, mg/dL	88.5 ± 6.6	91.8 ± 6.5	101.8 ± 26.1	110.1 ± 24.7	117.7 ± 27.5	128.7 ± 30.0	0.614*

* $p<0.001$ for trend.

Table 3. Comparisons in the entire sample between patients with and without a diagnosis of MetS (3+ components); patients with and without EDS

All patients (n=529)	No MetS (n=258)	Yes MetS (n=271)	ESS<10 (n=255)	ESS≥10 (n=274)
Age (yr)	48.1 ± 13.3	54.4 ± 11.0*	52.6 ± 13.1	50.1 ± 13.2*
Boby Mass Index (kg/m^2)	28.1 ± 4.9	33.7 ± 3.9*	30.3 ± 5.2	31.2 ± 6.6
Neck circumference (cm)	39.9 ± 3.6	43.1 ± 3.9*	41.3 ± 4.0	41.8 ± 4.2
AHI (events/h)	32.2 ± 22.1	54.0 ± 28*	40.3 ± 25.9	46.2 ± 28.9*
Arousal Index (events/h)	42.1 ± 19.3	60.4 ± 23.2*	49.5 ± 21.8	53.3 ± 24.3
Lowest SaO2 (%)	84.5 ± 7.7	77.1 ± 10.1*	82.0 ± 8.9	79.6 ± 9.7*
Epworth Sleepiness Score	9.4 ± 5.0	10.0 ± 5.1	5.3 ± 2.4	13.9 ± 3.0
Systolic blood pressure (mmHg)	124.0 ± 15.3	138.2 ± 16.6*	130.7 ± 18.0	131.5 ± 16.4
Diastolic Blood Pressure (mmHg)	75.8 ± 10.8	85.6 ± 12.2*	79.1 ± 11.7	80.8 ± 12.8
Waist circumference (cm)	100.1 ± 12.5	113.8 ± 12.3*	105.8 ± 13.0	108.4 ± 15.1*
HDL-Cholesterol (mg/dl)	58 ± 19	49 ± 16*	54 ± 18	53 ± 18
Triglycerides (mg/dl)	115 ± 54	189 ± 98*	151 ± 89	155 ± 87
Fasting Blood Glucose (mg/dl)	95.0 ± 19.3	115.8 ± 27.3	105.8 ± 13.0	108.4 ± 15.2

Asterisks indicate significant difference vs data reported in the previous column

Table 4. Summary of unadjusted and adjusted beta coefficients between each MetS component and OSA severity assessed as AHI or mean nocturnal SaO2

	AHI unadjusted	p	**Age, smoking and BMI**	p	**Age, smoking, BMI and gender**	p
Waist Circumference	1.067	<0.001	0.409	<0.001	0.258	NS
Systolic Blood Pressure	0.627	<0.001	0.414	<0.001	0.395	0.001
Diastolic Blood Pressure	0.752	<0.001	0.524	<0.001	0.495	0.001
Fasting Blood Glucose	0.214	<0.001	0.013	NS	0.012	NS
Serum Tryglicerides (log-transf)	10.401	<0.001	1.517	NS	0.575	NS
HDL-cholesterol	-0.161	0.02	-0.010	NS	0.037	NS

	Mean SaO2 unadjusted	p	**Age, smoking and BMI**	p	**Age, smoking, BMI and gender**	p
Waist circumference	-0.155	<0.001	-0.076	<0.001	-0.050	0.03
Systolic Blood Pressure	-0.056	<0.001	-0.020	0.03	-0.016	NS
Diastolic Blood Pressure	-0.069	<0.001	-0.039	<0.001	-0.033	0.006
Fasting Blood Glucose	-0.036	<0.001	-0.009	NS	-0.009	NS
Serum Tryglicerides (log-transf)	-1.952	<0.001	-0.599	0.04	-0.442	NS
HDL-cholesterol	0.037	<0.001	0.018	0.03	0.011	NS

Figure legends

Figure 1. OSA severity and number of MetS components. Patients with mild OSA (AHI<15) were often free of any MetS component (p<0.0001 by Chi-square test). Conversely, patients with severe OSA (AHI >30) had a MetS diagnosis (i.e., 3 or more components) more frequently than the other two groups (p<0.0001). Distribution of mild, moderate and severe OSA did not differ in patients with 1-2 MetS components (NS).

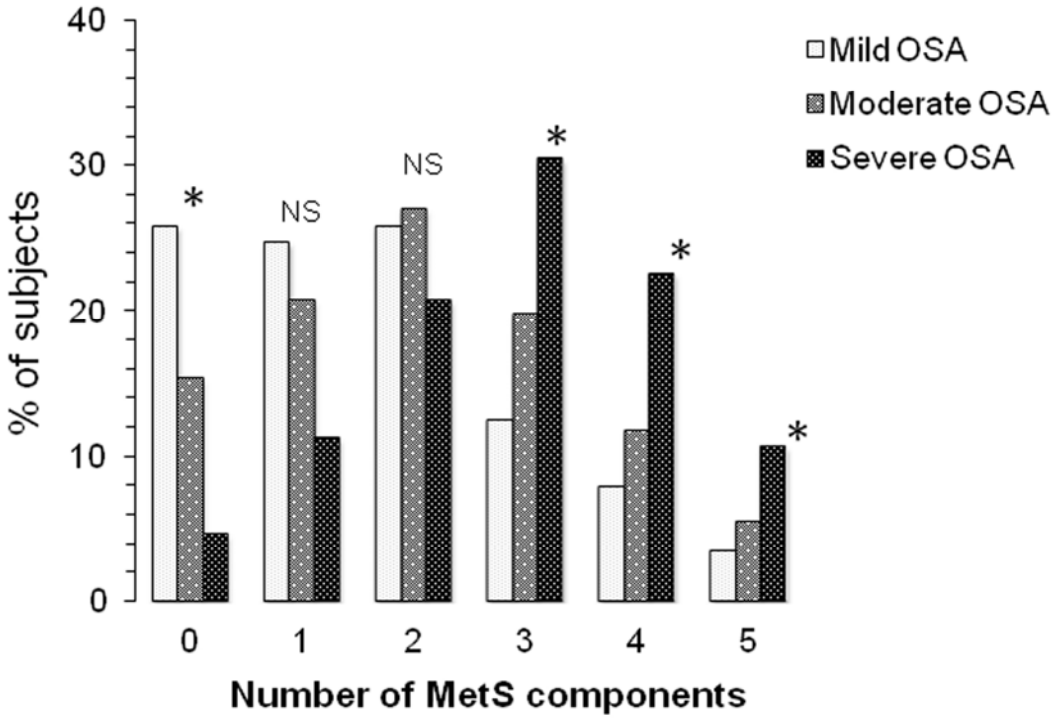
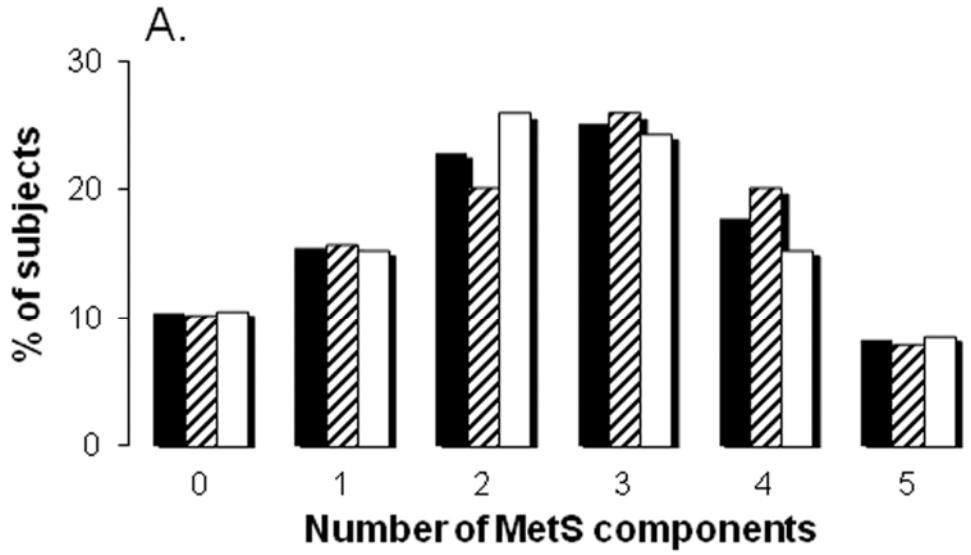


Figure 2. Distribution of the number of MetS components (panel A) and prevalence of each MetS component and of a MetS diagnosis (panel B) in the entire sample (black bars), and in patients with (hatched bars) and without (empty bars) EDS. No significant

difference was found between EDS+ and EDS- patients for any variable. WC: increased waist circumference; BP: elevated blood pressure; FBG: elevated fasting blood glucose; TG: elevated triglycerides; HDL-C: decreased HDL-Cholesterol.



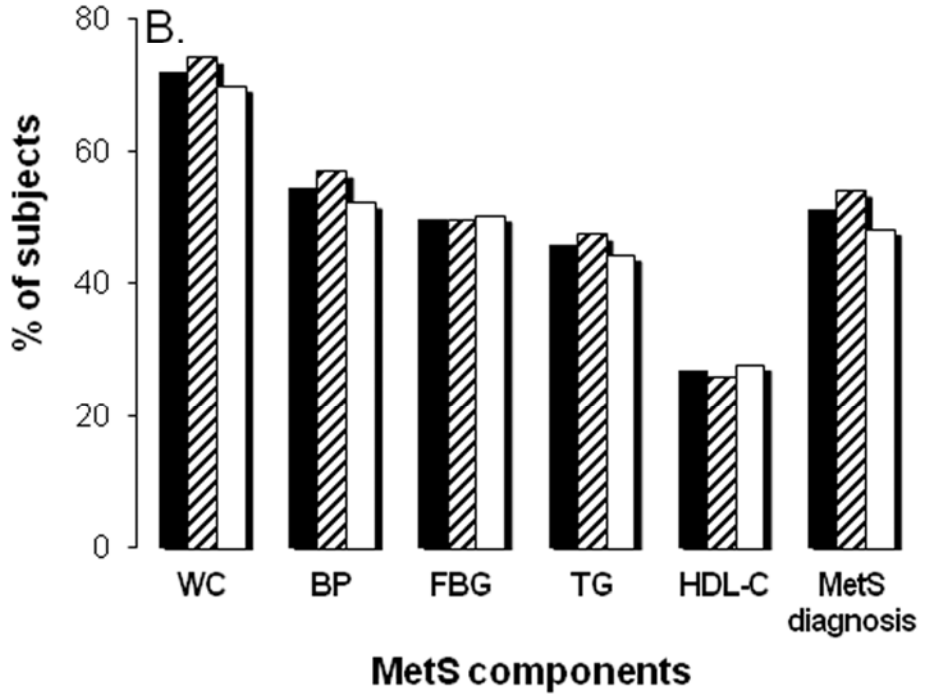


Figure 3. Insulin resistance, assessed as HOMA Index in 288 patients (black bars), linearly increased with the number of MetS components (Spearman's rho: 0.455, $p<0.001$). No significant differences were found between patients with (hatched bars) and without (blank bars) excessive daytime sleepiness (EDS). The numbers on top of columns indicate the number of subjects in each group.