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Obstructive Sleep Apnea and Metabolic Impairment In Severe Obesity

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ABSTRACT

Obstructive Sleep Apnea (OSA) seems to worsen metabolism. This effect has not evaluated in morbid obesity (MO). We hypothesized that the metabolic profile is more impaired in MO patients with OSA than in those without and investigated whether any specific metabolic dysfunction is related to OSA in MO.

A prospective multi-centre cross-sectional study was conducted in consecutive subjects before bariatric surgery. OSA was defined as apnea-hypopnea index (AHI)≥15 by overnight polysomnography (PSG). Anthropometrical, blood pressure (BP) and fasting blood measurements were obtained the morning after. Metabolic Syndrome (MetS) was defined according to NCEP ATPIII modified criteria.

159 patients were studied: 72% female, 72% OSA. MetS prevalence was 70% in OSA vs 36% in non-OSA ($p<0.001$). As AHI severity increased, metabolic parameters progressively worsened, even in those without type 2 diabetes (DM2). AHI was independently associated with systolic and diastolic BP, TG and HbA1c in the total sample and with systolic BP, cHDL and HbA1c in those without DM2. OSA increased the adjusted odds ratio of having MetS by 2.8 (95%CI 1.3 – 6.2, p 0.009).

In MO, OSA is associated with major metabolic impairment caused by higher BP and poorer lipid and glucose control, independent of central obesity or DM2.

Keywords: metabolic index, metabolic syndrome, morbid obesity, obstructive sleep apnea.

ABREVIATIONS LIST

AHI = apnea-hypopnea index

BMI = body mass index

BP = blood pressure

cHDL = high-density lipoprotein cholesterol

cLDL = low-density lipoprotein cholesterol

cVLDL = very low-density lipoprotein cholesterol

DM2 = Type 2 diabetes

ESS = Epworth Sleepiness Scale

EDS = Excessive Daytime Sleepiness

FBG = fasting blood glucose

FEV1% = predicted percentage of forced expiratory volume in the first second

FVC% = predicted percentage of forced vital capacity

HbA1c = the percentage of glycosylated hemoglobin

IGT = impaired glucose tolerance

MetS = metabolic syndrome

MO = morbid obesity

OGTT = oral glucose tolerance test

OSA = obstructive apnea-hypopnea syndrome

PaCO2 = partial arterial pressure of carbon dioxide

PaO2 = partial arterial pressure of oxygen

SpO2 = arterial oxygen saturation by pulse oximetry

TG = triglycerides

Time Sp02 <90%= mean percentage of sleep time with Sp02 below 90%

WC = waist circumference

INTRODUCTION

Metabolic abnormalities, whether assessed as Metabolic Syndrome (MetS) [1] or as their single components (central obesity, impaired glucose metabolism, hypertension,

hypertriglyceridemia and lower high-density lipoprotein cholesterol) have been shown to increase cardiovascular (CV) morbidity and mortality [2-5]. Central obesity seems to play a crucial role in the origin of metabolic disruption, but many other mechanisms have also been considered responsible [6]. Recent reports have suggested that OSA may worsen the effect of obesity on cardio-metabolic risk and that it could represent an additional burden on the metabolic dysfunction associated with obesity [7, 8].

The mechanisms through which OSA may worsen metabolism are complex. It may trigger several pathological mediating pathways (sympathetic activation, neurohumoral changes, glucose homeostasis disruption, inflammation and oxidative stress) through chronic intermittent hypoxia (CIH), and these may ultimately deteriorate the metabolic function [9, 10]. Animal studies have shown reduced insulin resistance and plasma lipids, as well as increased blood pressure (BP), after exposure of lean and obese animals to CIH [11], but the data in humans are scarcer.

Obesity is the main confounding factor in the investigation of the association between OSA and metabolic dysfunction [12]. Most previous reports have excluded subjects with morbid obesity (MO), possibly because the effect of OSA is expected to be little or absent in this subpopulation, due to extreme obesity. Conversely, MO patients could have a higher CV risk compared to non-MO subjects, because of the high prevalence of both metabolic dysfunction [13, 14] and OSA [15, 16]. Therefore, investigating this association in MO should contribute to a better understanding of the relative interaction between OSA, MO and metabolic dysfunction.

We hypothesized that, in a cohort of consecutive MO patients enrolled in a bariatric surgery program, the metabolic profile is more impaired in those with OSA than in those with no OSA. Furthermore, we attempted to detect whether there is any specific metabolic

dysfunction pattern related to OSA, and whether the overall CV risk increases in parallel with OSA severity in the morbidly obese.

METHODS

Subjects and protocol:

Consecutive patients prospectively included in the obesity surgery program were studied in the corresponding Sleep Units from January 2009 through February 2010. The study protocol was approved by the local Ethical Committee of each hospital (PR052/08, 07/064/797, PI080277). All participants gave their informed written consent.

Inclusion criteria were the same as those for the obesity surgery program: age between 18 and 60 years and a body mass index (BMI) $\geq$ 40 kg/m^2 or BMI $\geq$ 35 kg/m^2 with co-morbidity related to obesity (resistant hypertension, established heart disease, severe degenerative osteoarthritis, respiratory failure). The following were excluded: patients with known OSA and prior CPAP treatment, unstable cardiovascular conditions, acute or chronic inflammatory diseases during the previous 6 months, chronic immunosuppressant therapy, severe cognitive or psychiatric disorders, chronic obstructive pulmonary disease [17], pregnancy or past or current history of alcohol abuse, and those who refused their consent.

Each participant completed a detailed questionnaire on medical history, cardiovascular risk factors and current medication. Exercise level and sleep duration were recorded by a self-administered International Physical Activity Questionnaire (IPAQ) [18] and a sleep diary for 15 consecutive nights. Anthropometric characteristics included BMI, neck circumference (at the level of the laryngeal prominence), waist circumference (WC, measured midway between the lower rib and the iliac crest), waist/hip ratio and percentage of body fat mass measured with electrical bioimpedance (BIA 101, Akern Bioresearch, Florence, Italy). Clinical blood pressure (BP) was measured by a standard mercury sphygmomanometer while the subject was

seated at rest, taken the mean value of at least 2 measurements separated by 5 minutes; an additional measurement was made if there was a difference of more than 5 mmHg between the two [19]. Respiratory functional assessment included forced spirometry and arterial blood gas analysis, taken with the subject seated breathing room air.

Sleep Study:

OSA was determined by a full overnight polysomnography (PSG). PSG interpretation was assessed according to standard criteria [20], as described in Supplementary Material E1.

As few morbidly obese patients were expected to show an AHI < 5 events/hour[16], an AHI cut-off of 15 events/hour was chosen to define the presence of OSA by the study design. The degree of nocturnal desaturation was assessed by the mean percentage of sleep time with SpO_2 below 90% (Time SpO_2 < 90%). Excessive Daytime Sleepiness (EDS), quantified by the Epworth Sleepiness Scale (ESS), was defined as an ESS score ≥ 10.

Blood measurements and Metabolic Syndrome definition:

The morning after PSG, a venous blood sample was obtained from all patients in fasting conditions and an oral glucose tolerance test (OGTT) was performed, except in those with previously known type 2 diabetes (DM2). Fasting blood glucose (FBG), percentage of glycosylated hemoglobin (HbA1c), total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and very low-density lipoprotein (VLDL) cholesterol levels were determined with standard laboratory methods. Patients were classified according to the OGGT: normal glucose tolerance (post-load glucose <7.8 mmol/L), impaired glucose tolerance (post-load glucose 7.8-11.1 mmol/L) and established DM2 (post-load glucose ≥11.1 mmol/L) [21].

MetS was defined in accordance with the NCEP-ATP III modified criteria [1] as the presence of three or more of the following: WC ≥88 cm in women, ≥102 cm in men; high BP as systolic ≥130 and/or diastolic ≥85 mmHg or antihypertensive treatment; high FBG as ≥5.6

mmol/L or anti-diabetic treatment; high triglycerides as ≥1.7 mmol/L or lipid-lowering treatment; 5) reduced HDL-C as <1.3 mmol/L in men and <1 mmol/L in women or lipid-lowering treatment. Metabolic Index was established as the number of individual MetS components for each patient.

Cardiovascular risk assessment in the AHI categories

The Framingham Cardiac Risk Score was applied to estimate the CV risk [22] in the different AHI categories. The scores consider sex, age, total cholesterol, cHDL, systolic BP and smoking, and they were used to predict the 10-year risk of coronary events in the AHI categories.

Sample Size:

Power calculations indicated that 39 subjects were needed in each group to detect at least a difference of 0.32 in MetS prevalence between OSA and non-OSA, based on prior studies reporting high prevalence of MetS and OSA in MO [23] and similar MetS prevalence difference depending on OSA status [24], assuming an alpha risk of 0.05 and a beta risk of 0.20.

Statistical methods:

Data were expressed as mean ± standard deviation, median (interquartile range) or percentage for parametric, non-parametrical and categorical data, respectively. The bivariate comparisons were evaluated using the chi-square (categorical), Student's t (parametric) or Mann-Whitney tests (non-parametric). Multiple comparisons were evaluated using the chi-square test (categorical), ANOVA with Scheffe Post-hoc analysis (parametric) and the Mann-Whitney test, applying the Bonferroni method when significant differences were found by the Kruskal-Wallis test (non-parametric). The adjusted linear regression model studied the association between AHI and individual measures of metabolic dysfunction. Logistic regression assessed the relationship between MetS and OSA (AHI ≥15). The association results were summarized

using unadjusted and adjusted odds ratios (ORs) and β coefficients with their 95% confidence intervals (95% CIs). A p-value < 0.05 was considered statistically significant. The SPSS version 15 software (Chicago, IL, USA) was used for all the analyses.

RESULTS

A total of 174 consecutive patients were evaluated. Fifteen patients were excluded due to inflammatory disease (n=8), Chronic Obstructive Pulmonary Disease (n=3), pregnancy (n=1), immunosuppressant therapy (n=1) and refusal to participate (n=2). Thus, we collected 159 patients: 44 non-OSA and 115 OSA. The mean age was 43±10 years, the mean BMI was 46.1±5.8 Kg/m^2 and 72% of them were female.

OSA versus non-OSA group

OSA subjects were older, had a larger neck and WC and had a non- significant trend toward a higher BMI (Table 1). No differences were observed in sex predominance and OGGT categories. When stratifying by gender, the level of physical activity did not differ between OSA and non-OSA subjects (data not shown). For comorbidities, hypertension and diabetes were reported more frequently by OSA than by non-OSA patients (hypertension 48% vs 21%, p 0.002, diabetes 24% vs 11%, p 0.057). As regards medication, angiotensin receptor antagonists and oral hypoglycemic agents were prescribed more in OSA than in non-OSA group (12% vs 0%, p 0.015 and 22% vs 7%, p 0.027, respectively).

Table 1 also shows the main sleep characteristics of the total sample, and according to the presence/absence of OSA. Self-reported sleep duration was longer in OSA than in non-OSA but the PSG total sleep time was similar in both groups. OSA subjects had worse sleep parameters in terms of nocturnal oxygen desaturation levels and arousal index, but with no differences in the sleep stage percentages or in the level of EDS, according to the ESS.

Metabolic variables according to AHI categories

OSA patients had a more impaired metabolic profile than non-OSA patients (Table 2). They had higher levels of systolic and diastolic BP, FBG, HbA1c and TG, and lower levels of cHDL. Moreover, as the severity of OSA increased according to AHI categories, a progressive significant worsening of individual metabolic parameters was found and the Metabolic Index deteriorated. Moreover, the Framingham Cardiac Risk Score increased with the OSA categories (Figure 1).

The overall prevalence of MetS was 60% but was twice as high in the OSA, compared to the non-OSA group (70% vs 36%, $p < 0.001$). The prevalence of each individual MetS component was also higher in the OSA group but did not reach significance for reduced cHDL (41% vs 27%, p 0.112) (Figure 2).

We also examined the relationship between individual metabolic parameters and OSA markers by linear regression analysis (Table 3). In the unadjusted model, all metabolic parameters were associated with AHI and Time $SpO_2 < 90\%$ (data not shown). After adjusting for age, gender, smoking and BMI, the association with AHI remained significant for systolic BP, diastolic BP, TG and Hb1Ac, but was lost for FBG and cHDL. When adding WC to the adjustment, the associations did not change. Associations with ODI3% followed a similar pattern to those with AHI (data not shown). In contrast, when the same analysis was performed with Time $SpO_2 < 90\%$, only Hb1Ac and TG were significant; but after adjusting for WC, the association only remained significant for HbA1c.

Table 4 summarizes the results of binary logistic regression to assess the association of OSA and MetS in MO patients. Occurrence of OSA was defined as AHI ≥15, and the severity of nocturnal hypoxia by cumulative time at SpO2 <90% = 4.65% (as the median sample value). We also assessed the combination of both. After adjusting for age, gender, BMI and smoking, OSA increased the odds of having MetS threefold. The BMI did not appear to

contribute to the association since its exclusion during the statistical analysis did not change the results (data not shown).

OSA status according to metabolic variables

When we compared patients with (n=96) and without (n=63) MetS, the prevalence of OSA was significantly higher in the MetS group (83% vs 56%, $p < 0.001$). The distribution of the number of MetS components (Metabolic Index) significantly shifted toward high values in OSA, compared to non-OSA patients (Chi-square test, p-value 0.002, Figure 2).

Sub-analysis in patients without known type 2 diabetes

Since MetS is considered a pre-morbid condition for DM2, we repeated the analysis after excluding 33 patients with DM2 (reported in Supplementary Material E2).

Sub-analysis in females

Because our sample was mostly composed of women (n=115), we repeated the analysis for the female sub-group (reported in Supplementary Material E3).

DISCUSSION

To our knowledge, this is the first large cross-sectional study focusing on the association of OSA and MetS in MO. In agreement with our hypothesis, MetS was more prevalent, and the metabolic profile more impaired, in morbidly obese patients with OSA than in those without. The metabolic profile progressively worsened with increasing OSA severity, irrespective of gender. This worsening remained even after excluding those patients with DM2. Therefore, even in a population with such a high prevalence of MetS as morbidly obese patients, OSA is associated with a worse metabolic profile, suggesting a possible additional contribution to the increased CV risk associated with obesity.

The relationship between OSA and metabolic dysfunction has been studied mostly in moderately obese sleep-referred patient cohorts [9, 24-27], and more recently in specific high cardiovascular risk populations, such us MetS [7, 8, 28], hypertensive [29] and CV disease cohorts [30]. All these data agree that OSA is common in middle-aged moderately obese subjects and is associated with MetS or some of its components, independent of the BMI. We have chosen a different approach by studying severely obese patients who represent the extreme model of association between OSA, MetS and MO. Only a small retrospective study pointed out a higher prevalence of both disorders in the same bariatric cohort [23].

The comparison of OSA and non-OSA patients revealed a double prevalence of MetS (70% vs 36%, $p < 0.001$) and a progressively impaired metabolic profile in line with an increased AHI. Therefore, our data do not reinforce the notion that MO overwhelms the potential contribution of OSA to metabolic aggravation. Moreover, the occurrence of OSA still increased the adjusted odds of having MetS by up to threefold, irrespective of gender. This is a novel contribution because no analysis of the metabolic effect of OSA on MO females has been addressed before (see On-line supplementary material E3). Interestingly, in women it seems necessary to increase whole body fat in order to increase central fat; in contrast, this is not required in men. Also, the percentage of menopause state was higher in OSA, compared to non-OSA females, in keeping with three large cohort studies [31-33]; the association between OSA and MetS did not change, however, after adjusting for menopause state and percentage of body fat. Thus, it is plausible to consider that in morbidly obese patients, the metabolic dysfunction may be conferred not only by MO but also by OSA, which does not seem to have a gender specific effect.

Whether OSA is linked to a specific metabolic pattern has yet to be completely defined. In non-MO cohorts, OSA is associated with various metabolic abnormalities, probably due to the heterogeneity of the samples [24-27, 34, 35]. In the present study, a

significant linear association was found between AHI and systolic and diastolic BP, TG and HbA1c after controlling for BMI and WC. Furthermore, even in the subgroup of patients without diabetes, the association remained significant with systolic BP, cHDL and HbA1c. Thus, in MO patients, increasing severity of OSA is associated with metabolic worsening, caused mainly by higher systolic BP, lipid disruption and poorer glucose control, independent of adiposity and other confounders, and irrespective of established DM2.

Hypertension has been widely studied in OSA patients [36]. Recent guidelines on hypertension have recognized OSA as a frequent cause of secondary hypertension [37]. Our findings are consistent with previous large studies pointing to a high prevalence of hypertension among OSA patients [38-40]; more interestingly, a clear deterioration in BP levels in line with increasing OSA category was seen in this MO cohort, and higher BP is independently associated with OSA severity, regardless of gender or the degree of obesity.

As regards glucose metabolism, most published reports have found a significant association between OSA and hyperglycemia/insulin resistance/diabetes in moderate obese subjects [35, 41-43]. In the present study, although no differences in FBG or OGGT data were found when comparing the OSA and non-OSA groups, HbA1c was highly associated with OSA markers. So, even in the morbidly obese, our data showed a clear, graded inverse relationship between OSA severity and long-term glucose control, as assessed by HbA1c, after controlling for the degree of obesity and other confounders. This finding was also seen in patients without DM2.

The association between OSA and lipid profile has been less investigated. Overall, there is no definitive evidence regarding the effect of OSA on the lipid profile. The majority of cross-sectional studies are negative [26, 44-46], although some large sample studies found a positive association between OSA and higher TG and lower cHDL [24, 47, 48]. Our data

also show, for first time in a cohort of MO patients, an independent association of AHI with higher TG and lower cHDL.

Furthermore, although the Framingham study's generalization of CV risk in MO patients should be interpreted with caution, our data suggest that OSA may contribute an additional burden to CV morbidity and mortality in this cohort, and it should be controlled in any study evaluating the consequences of MetS in the morbidly obese.

Experimental studies in animals and humans have shown intermittent hypoxia to be a major determinant of metabolic dysfunction associated with OSA [49, 50]. In our cohort, OSA compared to non-OSA patients had a greater degree of nocturnal chronic intermittent hypoxia (CIH), due to higher AHI, Time $Sp0_2$ <90% and arousal index without higher subjective EDS or differences in sleep-stage percentages. Furthermore, AHI was independently associated with most of the individual metabolic parameters, according to the linear regression analysis, whereas Time SpO_2 < 90% was independently associated with only HbA1c. This may suggest that OSA contributes to metabolic dysfunction in MO, mostly through CIH. Moreover, adding a greater nocturnal hypoxemia by means of greater Time $Sp0_2$ <90% to a high baseline AHI leads to greater metabolic dysfunction than a high baseline AHI alone, according to the logistic regression analysis. These findings concur with those observed by Polotsky et al [51], supporting the "two-hit" model hypothesis to explain the potential role of OSA in the development of steatohepatitis and IR in severe obesity. MO might act as a "first hit" initiating a metabolic dysfunction and severe OSA through nocturnal chronic intermittent hypoxia may act as a "second hit" aggravating the disorder. Despite strong evidence from experimental studies demonstrating the role of CIH [11], a definitive causal role of OSA in metabolic impairment in humans cannot be firmly established. In interventional studies, CPAP therapy lowered BP [52], while data on glucose and/or lipid control appear to still be inconclusive [53-57]. Thus, further long-term randomized controlled

interventional trials are clearly needed in well-characterized samples, and also in the morbidly obese, in order to address the direction of causality.

Adipose tissue, besides from being the main energy storage organ, is a highly active tissue involved in the integrated metabolism regulation [58]. Ectopic fat, particularly visceral fat, could adversely modify the metabolism, decreasing the insulin sensitivity in key tissues by a paracrine effect and through the release of adipokines that promote a low-grade pro-inflammatory state [59]. OSA may worsen this state [60] by acting as an additional cardiometabolic burden risk. . In the present study we have used WC as an accepted surrogate of visceral adiposity [61]. OSA patients had greater WC and NC compared to non-OSA ones despite similar BMI and fat mass percentage, suggesting that OSA is more closely linked to a particular visceral adiposity than to the overall obesity. Conversely, the association of OSA with several metabolic abnormalities remained independent of WC and gender, supporting the notion that OSA may play an additional role in the overall metabolic dysfunction, even in MO. Unfortunately, direct analysis of visceral fat was not possible in this study and thus our findings should be considered approximate. Despite this limitation, these results concur with the hypothesis previously proposed by Vgontzas et al [62]: visceral fat could progressively worsen MetS and OSA manifestations but OSA may also aggravate MetS through an increase in sympathetic activation, inflammation and insulin resistance that deteriorates the overall metabolic dysfunction.

In our cohort, OSA prevalence was notably high: 72% of patients had an AHI ≥15 and only 2% had an AHI <5. Significantly, most subjects did not complain about EDS (72% of OSA patients had ESS<10), even if they had severe OSA. Although previous studies demonstrated objectively higher EDS in obese patients, compared to healthy non-obese controls, regardless of OSA status [63, 64], the lack of sleepiness measured by EES is concordant with previous studies evaluating patients before bariatric surgery. This point may

reflect the limitations of the EES in the MO population, as there are other potential co-factors that could affect EDS [65, 66]. Our finding of a lack of subjective sleepiness is clinically relevant, however, since it emphasizes the need to perform sleep studies in this specific population, regardless of self-reported symptoms.

As limitations, the cross-sectional study design does not provide cause-effect evidence, although the regression analysis showed an independent association between OSA markers and individual parameters of dysfunction. Also, it would have been desirable to perform abdominal CT or MR to assess the amount of visceral fat but the subjects did not fit into the machines due to their high body weights. Finally, as discussed, we did not assess objective EDS.

Conclusions

OSA is associated with a more severe metabolic profile in morbidly obese patients, independent of age, gender, BMI and smoking, suggesting an important role of OSA in addition to obesity, in the pathogenesis of metabolic dysfunction in this population. Since OSA is a treatable condition, and EDS assessed by ESS is not a good OSA marker in MO, clinicians dealing with obese subjects should appropriately assess OSA in addition to other classic known obesity-related comorbidities, in order to better treat the overall metabolic dysfunction.

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Figure 1

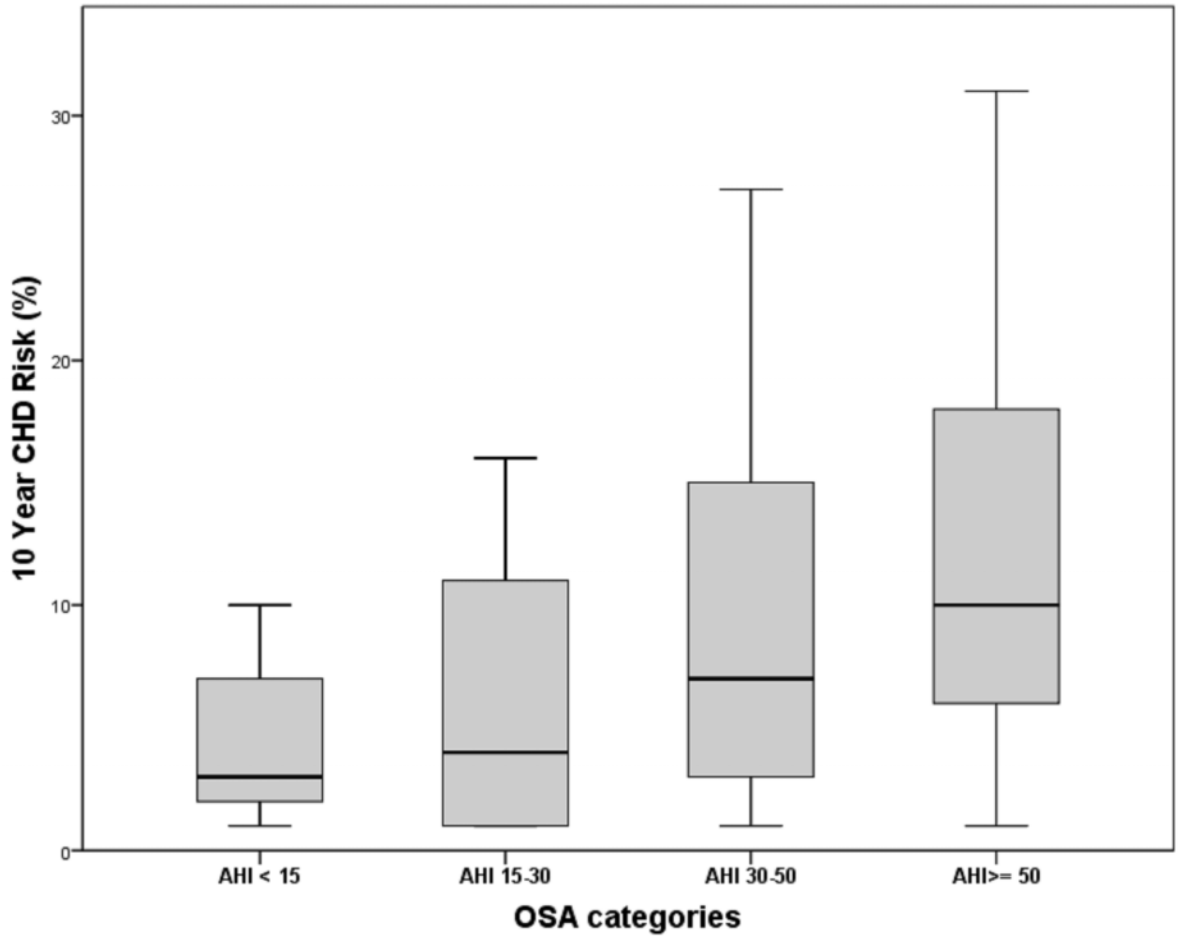
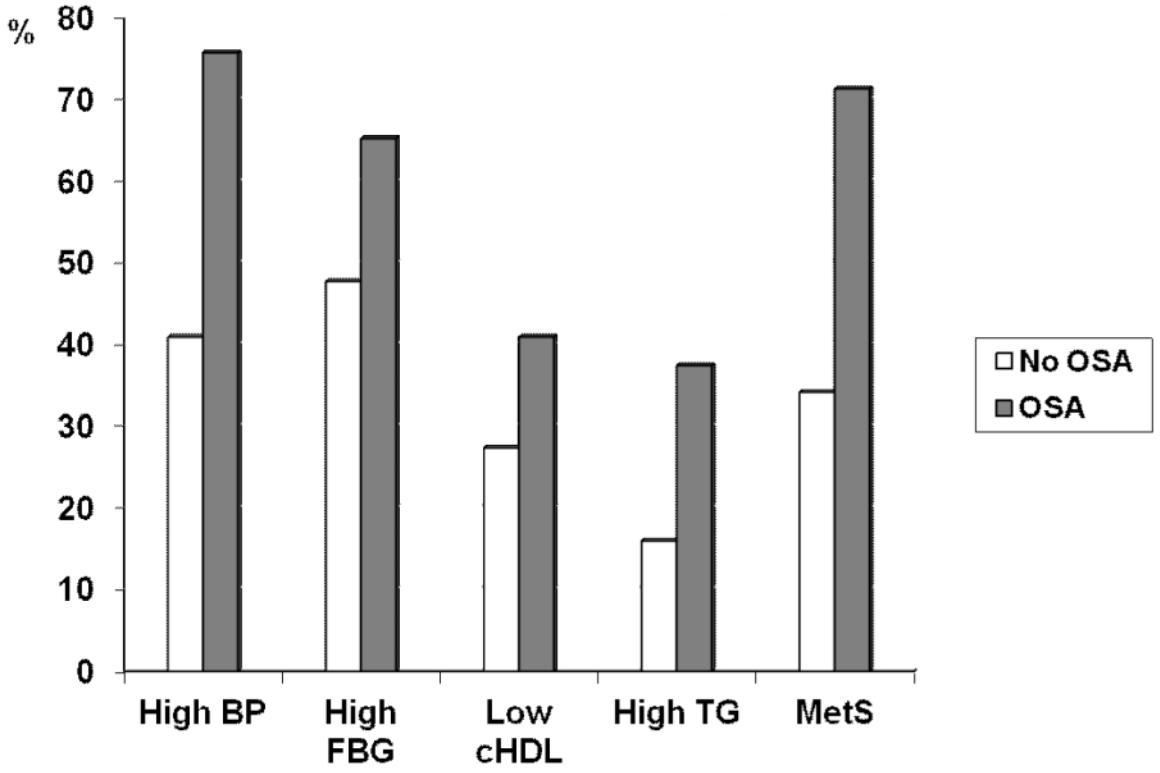


Figure 2


%
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50
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30
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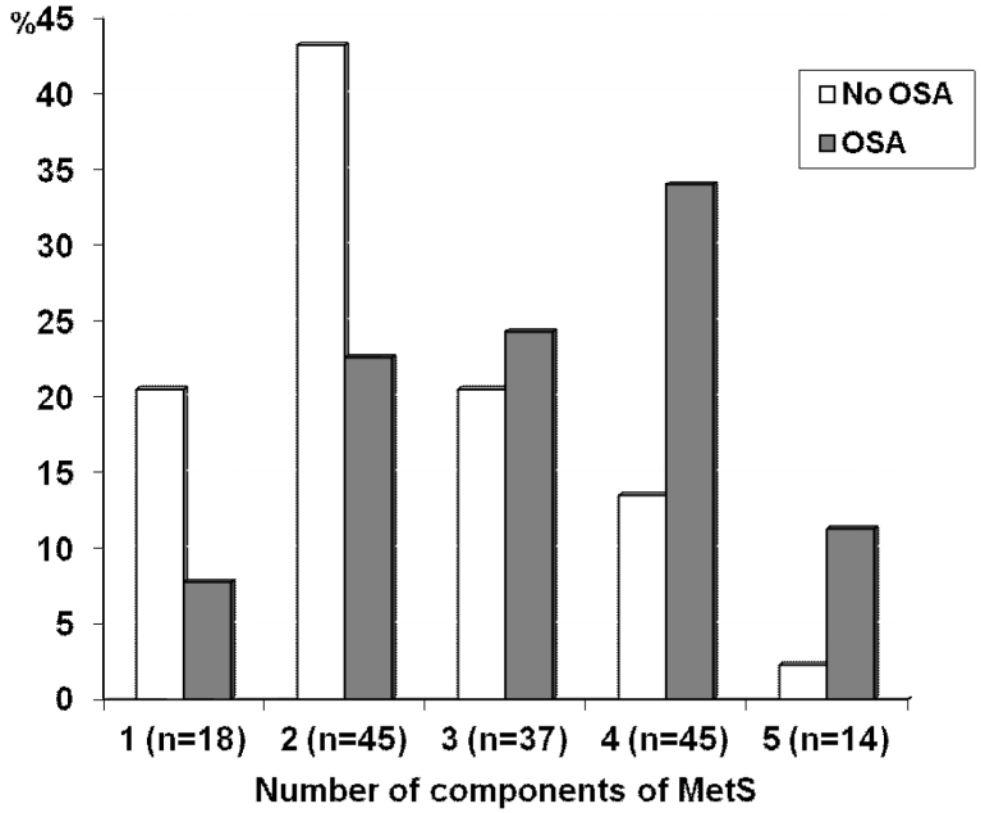
10
0
High BP
High FBG
Low cHDL
High TG
MetS
No OSA
OSA

Figure 3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10
5
0
1 (n=18)
2 (n=45)
3 (n=37)
4 (n=45)
5 (n=14)
Number of components of MetS
No OSA
OSA