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Original article

Obstructive sleep apnoea syndrome and the metabolic syndrome in an internal medicine setting

Francesco Angelico [a,*], Maria del Ben [a], Teresa Augelletti [a], Rosanna de Vita [b], Rocco Roma [b], Francesco Violi [a], Mario Fabiani [b]

[a] Department of Experimental Medicine, University La Sapienza, Rome, Italy
[b] Department of Neurology and Otorinolaringoiatrics, University La Sapienza, Rome, Italy

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ABSTRACT

Background: Obstructive sleep apnoea syndrome (OSAS) is widely accepted as a cardiovascular risk factor. Lately it has been considered in turn as both a component and one of the causes of the metabolic syndrome (MS).
Methods: We studied 281 heavy snorers of both sexes consecutively attending a metabolic clinic. Aim was to evaluate the association of OSAS and MS in a large series of patients within an internal medicine setting. Patients underwent a clinical and biochemical work up and performed unattended polysomnography.
Results: Of 226 non-diabetic snorers, 48 had primary snoring; 54 mild, 51 moderate, and 73 severe OSAS. A positive association was found between OSAS severity, central obesity indices and the mean metabolic score ($p=0.016$). Prevalence of hypertension increased with OSA severity ($p=0.010$). Polysomnographic indices were correlated with the metabolic score, insulin levels and central obesity indices.
At regression analysis, male sex ($t=3.92$; $p=0.000$) and waist circumference ($t=3.93$; $p=0.000$) were independently associated with AHI (apnoea/hypopnoea index), while ODI (oxygen desaturation index) and waist circumference were the independent predictors ($t=2.16$; $p=0.033$ and $t=3.74$; $p=0.000$ respectively) of the metabolic score.
Prevalence of OSA was 83% in 55 patients with diabetes and 34% had severe OSA. Almost all diabetics with OSA had MS. The metabolic score was higher in diabetic OSA as compared to non-diabetic OSAS ($p=0.000$).
Conclusions: Our findings show a high prevalence of OSAS among patients referred to a metabolic outpatient clinic because of suspected metabolic disorders and heavy snoring and suggest a strong bidirectional association between OSAS and MS.

1. Introduction

Obstructive sleep apnoea syndrome (OSAS) is a common nocturnal disorder affecting 2–4% of men and 1–2% of women in the general adult population [1]. OSAS is clinically characterized by recurrent episodes of partial or complete cessation of breathing during sleep, sleep fragmentation, heavy snoring and daytime sleepiness. Patients with OSAS have a higher incidence of arterial hypertension, coronary heart disease, cerebrovascular disease, and rhythm/conduction disorders [2]. Besides, severe OSAS compared to non-OSAS plays an independent role in atherosclerosis progression and is a risk factor for cardiovascular mortality and total mortality [2–6].

Patients with OSAS are often overweight and obese and they frequently present the clinical features of the metabolic syndrome (MS), also called insulin-resistance syndrome, an emerging disorder associated with accelerated atherosclerosis [7–9]. The majority of OSAS patients show the cluster of metabolic and non-metabolic cardiovascular risk factors of MS, i.e. abdominal obesity, atherogenic dyslipidaemia, raised blood pressure, insulin resistance +/− glucose intolerance, proinflammatory state and prothrombotic state suggesting that OSAS may be a further manifestation of MS [10]. However, it is also possible that OSAS might directly contribute to the development of insulin resistance and the other cardiovascular risk factors found in patients with MS. There is a strong evidence that OSA is an independent risk factor for systemic hypertension [11–13]. Several reports have found increased insulin resistance and impaired glucose tolerance in OSAS patients, independent of body weight [14–19]. Moreover, in a recent longitudinal study performed in Western Australia, moderate–severe OSA was a significant univariate and independent risk factor for incident type 2 diabetes and all-causes mortality [6]. Finally, experimental studies also suggest a role of intermittent hypoxia in the pathogenesis of hyperlipidaemia, supporting an independent role of OSAS, in addition to obesity, in the

* Corresponding author. Department of Experimental Medicine, Division of Internal Medicina C; Policlinico Umberto 1, Via Antonio Nibby 8, 00161 Rome, Italy. Tel./fax: +39 06 44234029.
E-mail address: francesco.angelico@uniroma1.it (F. Angelico).

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pathogenesis of non-alcoholic steatohepatitis [20]. The above data support a model of bidirectional association between OSA and MS. Indeed, visceral obesity and the cluster of the metabolic risk factors may lead to OSA, which, in turn, may accelerate these metabolic abnormalities, possibly through the induction of inflammation and oxidative stress.

Most published reports refer to male patients studied in Sleep Disorders Clinics.

The aim of the study was to test the hypothesis of a strong association of OSAS and MS in a large series of patients of both sexes within an internal medicine setting.

2. Material and methods

2.1. Patients

The study group consisted of 281 consecutive patients who were referred between January 2007 and December 2009 to our metabolic outpatients clinic because of suspected metabolic disorders with heavy snoring and possible OSAS. All patients had a complete clinical and biochemical work up as part of routine clinical examination.

Written consent was obtained from all subjects before the study and the study conforms to the ethical guidelines of the 1975 Declaration of Helsinki. To be eligible for the study, patients had to fulfil the following criteria: no history and clinical signs of heart failure, autoimmune disease, acute inflammatory disease, or any severe disease shortening life expectancy, such as diagnosed cancer, chronic liver disease, and severe renal disease.

Following the new National Cholesterol Education Program Adult Treatment Panel III criteria [8], MS was diagnosed by the concomitant presence of at least three of the following five clinical features: central obesity (defined as waist circumference ≥102 cm for men and ≥88 cm for women), fasting blood glucose ≥100 mg/dl or drug treatment for increased blood glucose levels, triglycerides ≥150 mg/dl or drug treatment for increased triglyceride levels, HDL-cholesterol <40 mg in men and <50 mg/dl in women/dl, arterial systolic/diastolic blood pressure ≥130/≥85 mm/Hg or drug treatment for increased blood pressure. A metabolic score was calculated for each patient based on the number of the discrete components of MS identified.

Arterial blood pressure was measured on the right arm with the subjects in a sitting position and after a 5-min rest, using a mercury sphygmomanometer: the average of two measurements, 1 min apart, was considered. Waist circumference, height and weight were recorded with subjects wearing light clothing, without shoes and body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Diabetes was diagnosed in 53 diabetics, according to the American Diabetes Association criteria [21]. Subjects taking insulin or oral antidiabetic drugs were considered to have diabetes.

2.2. Blood sampling protocol

Fasting venous blood samples were taken in the supine position on the morning after performing polysomnography and stored at −80 °C until assay. Subjects underwent routine biochemical evaluation including fasting total and HDL-cholesterol, triglycerides, glucose and insulin. Serum total cholesterol, HDL-cholesterol and triglycerides were measured by an Olympus AN 560 apparatus using an enzymatic colorimetric method. LDL-cholesterol levels were calculated according to the Friedwald formula [22]. Plasma insulin levels were assayed by commercially available radioimmunoassay. The homeostasis model assessment (HOMA-IR) was used to estimate insulin resistance using the formula: glucose (mmol/l) × [insulin (mU/l)/22.5] [23].

2.3. Polysomnography (nocturnal recording)

Patients underwent unattended overnight home polysomnography using an overnight home sleep recording (Embletta, PDS; Medcare, Reykjavik, Iceland). The device recorded nasal and oral airflow, chest and abdominal movement, pulse oximetry, body position and snoring noise. The sleep recordings were downloaded to a computer and scored by a principal investigator. A minimum of 5 h of recording was accepted to be adequate for scoring. The presence and severity of apnoea was assessed based on the number of apnoea/hypopnoea episodes per hour of sleep (apnoea/hypopnoea index AHI). Apnoea was defined as continuous cessation of airflow for more than 10 s and hypopnoea was defined as reduction of airflow for more than 10 s with oxygen desaturation of ≥4% and arousal. OSAS was defined as an AHI of ≥5. Patients were categorized into four subgroups according to OSA severity, as follows; normal AHI <5 events/h; mild OSA, AHI ≥5 to <15 events/h; moderate OSA, AHI ≥15 to <30 events/h; severe OSA, AHI ≥30 events/h.

Patients had overnight home pulse oximetry monitoring with a transcutaneous fingertip sensor connected via cable to an Ohmeda Biox 3700 pulse oximeter (Louisville, CO). Oxygen desaturations were defined as a decrease in oxygen saturation ≥4% during a 10-s period, compared with the previous 10-s period. The oxygen desaturation index (ODI) was calculated as the total number of oxygen desaturations divided by the reported time of sleep in hours. According to ODI severity, patients were divided in four ODI categories: normal ODI <5 events/h; mild: ODI ≥5 to <15 events/h; moderate, ODI ≥15 to <30 events/h; severe, ODI ≥30 events/h. The mean haemoglobin oxygen saturation level (SaO_2) in total sleep time was also calculated.

2.4. Statistical analysis

Statistical analysis was performed by using the SPSS statistical software version 11.0 for Windows (SPSS, Inc., Chicago, Illinois). All variables were tested for normal distribution prior to analyses. Data are expressed as the mean ± SD for continuous variables. The correlation between variables was analyzed with the Pearson and the Spearman tests. Student's *t*-test for unpaired data was used for the comparison of mean values. Group comparisons were performed by use of analysis of variance and test for linear trend in One-way ANOVA. Proportions and categorical variables were tested by the χ^2-test and by the 2-tailed Fisher's exact method when appropriate. Mantel–Haenszel chi-square test was used to assess linear-by-linear associations. Multiple linear regression analyses were performed using a stepwise selection method to determine the independent predictors of AHI and or ODI. All *p*-values are two-tailed; a *p*-value of less than 0.05 was considered statistically significant.

3. Results

Fifty-five patients out of the 281 who performed overnight polysomnography were found to have diabetes mellitus and were analyzed separately. Out of the remaining 226 non-diabetics, 48 had primary snoring and 178 (78.6%) had a positive polysomnography for OSA: 54 had mild, 51 moderate and 73 severe OSA.

Clinical and metabolic characteristics of non-diabetic patients with OSA by severity and control snorers are reported in Table 1. A strong positive association was observed between OSA severity and the indices of central obesity, i.e. body mass index ($p = 0.003$) and waist and hip circumferences ($p = 0.000$ and $p = 0.001$, respectively). In addition, a positive association was seen with the male sex: more precisely, 87.7% of patients with severe OSA were males. Furthermore, a positive linear increase ($p = 0.016$) of the mean metabolic score was observed with the worsening in OSA severity.

Table 2 shows the prevalence of MS and its components in patients with different severity of OSAS. A statistically significant increase in

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Table 1
Clinical and metabolic characteristics of patients with OSA and in controls.

	OSA				p
	Snorers	Mild	Moderate	Severe	
	AHI<5	AHI 5–14	AHI 15–29	AHI≥30	
	n=48	n=54	n=51	n=73	
Age	49.8±10.9	51.0±12.3	57.4±10.2	53.0±11.4	0.005
Males (%)	60.4	68.5	80.0	87.7	0.003
AHI (events/h)	1.5±1.6	10.4±2.5	22.2±3.6	53.3±17.8	0.000
Average SaO_2	95.3±1.3	94.1±2.1	93.6±1.7	89.0±11.7	0.000
ODI (events/h)	4.1±5.5	13.5±14.1	20.2±14.4	46.5±22.4	0.000
Body mass index (kg/m^2)	29.2±3.8	31.6±5.2	31.2±6.7	33.2±6.0	0.003
Waist circumference (cm)	101.2±9.8	108.2±13.1	107.0±12.3	113.7±13.9	0.000
Hip circumference (cm)	106.8±8.7	113.2±12.2	110.3±13.4	115.6±12.3	0.001
Waist/hip ratio	0.94±0.07	0.95±0.08	0.97±0.05	0.98±0.05	0.027
Blood glucose (mg/dl)	96.6±13.7	95.5±12.8	92.2±15.2	93.9±13.8	0.428
Insulin (μU/ml)	13.9±6.5	19.7±24.0	16.2±9.7	20.0±15.6	0.148
HOMA-IR	3.4±1.8	4.8±5.5	3.7±23	4.7±3.7	0.158
Total cholesterol (mg/dl)	210.3±41.9	204.5±36.8	208.9±41.9	207.8±38.9	0.900
LDL-cholesterol (mg/dl)	135.2±40.4	130.0±34.4	134.3±35.5	132.8±33.0	0.888
HDL-cholesterol (mg/dl)	46.4±12.3	46.0±8.2	46.±14.2	42.5±9.5	0.153
Triglycerides (mg/dl)	143.2±114.5	142.3±76.1	141.8±65.7	162.2±108.9	0.558
SCORE metabolic syndrome	2.1±1.2	2.3±1.3	2.3±1.1	2.7±1.1	0.016

the prevalence of MS was observed from snorers to subjects with severe OSAS ($p=0.012$). A positive, statistically significant linear association ($p=0.010$) was found between prevalence of hypertension and OSAS severity, while prevalence of hypertriglyceridemia, low HDL-cholesterol and central obesity showed only a positive trend.

Table 3 shows the correlations between AHI, ODI and average SaO_2 and some clinical and metabolic characteristics. All indices were strongly correlated with the metabolic score, with insulin serum levels and with the indices of central obesity. A positive, statistically significant correlation was also observed between HOMA-IR and ODI ($p=0.009$) and average SaO_2 ($p=0.000$).

Several multiple regression models were constructed to evaluate in the study sample the independent predictors of AHI, ODI and SaO_2. We initially tested covariates that may have had clinical relevance and those that showed univariate associations. In the final regression model, male sex ($t=3.92$; $p=0.000$) and waist circumference ($t=3.93$; $p=0.000$) were the only variables independently associated with AHI. Conversely, HOMA-IR was the only independent predictor of ODI ($t=2.42$; $p=0.018$) and waist circumference the only variable independently associated with the average SaO_2 index ($t=-3.42$; $p=0.001$).

Table 4 reports polysomnographic data in patients with and without MS. Prevalence of severe OSA was significantly higher in MS patients ($p=0.045$). MS patients had higher mean ODI ($p=0.000$) and lower mean SaO_2 index (0.015) than those without MS. A multivariate analysis was performed to evaluate the independent predictors of the number of metabolic syndrome parameters in the entire population. Regression analysis showed that ODI was the independent predictor ($t=2.16$; $p=0.033$) of the metabolic score, together with waist circumference ($t=3.74$; $p=0.000$).

Prevalence of OSA was 83% in 55 patients with type 2 diabetes mellitus and 34% had severe OSA. Some clinical and metabolic characteristics of diabetic and non-diabetic OSA patients are reported in Table 5. Almost all diabetics with OSA had metabolic syndrome, while only 54% of non-diabetic OSA reached the criteria for this diagnosis. More than 90% of diabetics had hypertension and central obesity. The metabolic score was significantly higher in diabetic OSA as compared to non-diabetic OSA ($p=0.000$).

4. Discussion

This is a large cross-sectional study showing a strong association between OSAS, MS and its clinical and metabolic components in subjects

Table 2
Prevalence of the metabolic syndrome and its components in patients with different severity of OSA.

	OSA				p
	Snorers	Mild	Moderate	Severe	
	AHI<5	AHI 5–14	AHI 15–29	AHI≥30	
	n=48	n=54	n=51	n=73	
Hypertension*	48.9	64.4	81.7	84.8	0.010
Central obesity*	74.5	77.8	73.5	86.6	0.077
Hypertriglyceridemia*	25.5	33.3	36.7	42.3	0.061
Low HDL-cholesterol*	31.9	25.9	38.8	45.2	0.051
Hyperglycemia*	38.3	31.5	24.5	25.7	0.121
Metabolic syndrome*	42.6	44.3	55.1	60.6	0.027

*According to ATPIII criteria.

Table 3
Spearman rank order correlation coefficients between AHI, ODI, and average SaO_2 and clinical and metabolic characteristics.

	AHI		ODI		Average SaO_2	
	r	p	r	p	r	p
Age	0.097	0.149	0.097	0.084	−0.198	0.011
AHI (events/h)	–	–	0.864	0.000	−0.591	0.000
Average SaO_2	−0.591	0.004	−0.648	0.000	–	–
ODI (events/h)	0.864	0.000	–	–	−0.648	0.000
Body mass index (kg/m^2)	0.206	0.002	0.267	0.001	−0.357	0.000
Waist circumference (cm)	0.304	0.000	0.307	0.000	−0.369	0.000
Hip circumference (cm)	0.227	0.001	0.246	0.004	−0.280	0.000
Waist/hip ratio	0.195	0.004	0.214	0.012	−0.215	0.007
Systolic blood pressure (mm/Hg)	0.098	0.148	−0.019	0.828	−0.229	0.006
Diastolic blood pressure (mm/Hg)	0.123	0.070	−0.038	0.656	−0.183	0.021
Blood glucose (mg/dl)	−0.131	0.052	−0.051	0.545	−0.085	0.286
Insulin (μU/ml)	0.150	0.031	0.266	0.002	−0.281	0.001
HOMA-IR	0.111	0.112	0.222	0.009	−0.283	0.000
Total cholesterol (mg/dl)	−0.043	0.525	−0.060	0.483	−0.026	0.748
LDL-cholesterol (mg/dl)	−0.050	0.463	−0.107	0.206	0.016	0.843
HDL-cholesterol (mg/dl)	−0.188	0.005	−0.129	0.129	0.106	0.183
Triglycerides (mg/dl)	0.079	0.244	0.116	0.169	−0.196	0.013
SCORE metabolic syndrome	0.148	0.029	0.166	0.049	−0.258	0.002

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Table 4
Prevalence of OSA and polysomnographic data in patients with and without metabolic syndrome.

	Metabolic syndrome		p
	Yes	No	
	n = 118	n = 108	
Age (years)	54.0 ± 11.0	51.5 ± 11.9	0.114
Males (%)	75.7	75.7	1.000
OSA (%)	82.5	74.8	0.109
Severe OSA (%)	37.7	26.2	0.045
AHI (events/h)	27.5 ± 23.1	22.3 ± 23.1	0.099
ODI (events/h)	31.2 ± 23.9	14.4 ± 17.3	0.000
Average SaO_2	92.0 ± 8.6	94.4 ± 1.8	0.015

of both sexes examined in an internal medicine setting. Prevalence of OSA was higher in MS patients as compared with those without. Patients with severe OSA were more obese, more hypertensive and more insulin resistant than those with a less severe OSA and control snorers. Polysomnographic indices – AHI, ODI and average SaO_2 – were independent predictors of central obesity, serum insulin and the metabolic score. In particular, an independent association was found between ODI and insulin resistance (HOMA-IR), which is generally believed to play a central role in the clustering phenomenon of CVD risk factors that defines MS [9].

Our findings are consistent with previous studies performed in Sleep Disorders Clinics demonstrating the vicious cycle fed by OSAS and MS, although the association between OSA, MS and insulin resistance remains controversial. In a retrospective review of 250 consecutive patients referred to a Sleep Disorders Center in the US [24], prevalence of MS was significantly higher in patients with OSA. In addition, an independent association between OSA and insulin resistance was also observed in 270 subjects consecutively referred for polysomnography in Hong Kong [8] and in a study of 98 suspected-OSA male patients in Tel Aviv [14]. Moreover, in a study performed in 213 Japanese patients with OSA, insulin resistance was seen to be associated to sleep-disorder breathing independent of obesity [16]. Finally, a significant improvement in insulin sensitivity as soon as two days after onset of effective CPAP therapy has been reported in most OSA patients [17], suggesting OSA as an independent risk factor for insulin resistance. Conversely, in a cross-sectional analysis of a male consecutive subjects referred to a sleep laboratory in UK, OSAS was independently associated with MS driven largely by increased serum triglyceride, elevated glucose and daytime sleepiness but not with insulin-resistance state [25].

However, in patients with OSA, other mechanisms other than insulin resistance may play a role in the pathophysiology of MS. Indeed, in our study, the analysis of MS components showed that hypertension was the primary variable associated with a diagnosis of OSA. In fact, prevalence of hypertension (according to ATP III criteria) was almost twice in patients with OSA compared to non-OSA patients (91.3% vs 57.1%; $p = 0.041$).

In keeping with our results, a retrospective analysis of 250 patients referred to a Sleep Disorders Clinic to have polysomnography, showed hypertension to be the only component of MS associated with a diagnosis of OSA, even if a positive association was seen between the severity of OSA and the presence of MS [18].

Our results are also consistent with results of the community-based Sleep Heart Health Study, which suggested an independent association between sleep apnoea and hypertension in middle-aged and older individuals of different sexes [26].

A dose–response association between sleep-disordered breathing at baseline and the presence of hypertension four years later, that was independent of known confounding factors, was found in 709 participants of the Wisconsin Sleep Cohort Study [11]. Furthermore, there is a growing experimental evidence that OSA can cause blood pressure rise, by increasing the activation of the renin–angiotensin-system [12]. This hypothesis has been strengthened by evidence from intervention trials, showing that treatment with continuous positive airway pressure may lower both systolic and diastolic blood pressures [13,27,28]. All the above findings suggest that OSA is likely to be a risk factor for hypertension and consequent cardiovascular morbidity in the general population.

It is largely accepted that obesity, and in particular visceral obesity, is strictly connected with OSA. In the present study the prevalence of visceral obesity in non-diabetic OSA patients was 80.9% and increased with the worsening of OSA severity, reaching 86.6% in patients with AHI>30. Apnoea–hypopnoea episodes and oxygen desaturation have been correlated to narrowed upper airway dimensions, due to the fatty tissue deposits within the airway walls, which increase the collapsibility of the pharyngeal lumen. Visceral obesity, however, is also associated to MS and insulin resistance, which in turn may induce OSA [29]. Thus, it seems actually hard to define which is the cause and which the consequence.

In our study almost all diabetic patients had OSA (83%). It is noteworthy that more than 90% of diabetic OSA patients satisfied the criteria for MS and were affected by hypertension and central obesity, while the corresponding figures in non-diabetic OSA were 54.0%, 67.8% and 80.9% respectively. These findings suggest that OSA patients with diabetes mellitus have a significantly higher cardiovascular risk profile.

It has been proposed that OSA and type 2 diabetes mellitus may be associated independently of the degree of adiposity and that OSA may be a risk factor for diabetes mellitus [19,30–32]. In addition, a community-based longitudinal study [6] in Western Australia, showed that moderate–severe OSA was a significant risk factor for the 4-year incidence of diabetes mellitus, even if the authors recognize that further studies are needed. Several pathophysiologic mechanisms have been proposed to explain the alterations in glucose metabolism in OSA patients. Intermittent hypoxia, endothelial dysfunction, inflammatory state, sleep fragmentation and high sympathetic nervous system activity, all can play a pivotal role in the dysregulation of glucose control.

In conclusion, our findings show a high prevalence of OSAS in patients with suspected metabolic disorders and heavy snoring and suggest the presence of a strong association between OSAS and MS; they also suggest a bidirectional association between the two conditions, although direct causality between the two has not been demonstrated yet. Indeed, insulin resistance, MS and its clinical and metabolic features may induce OSAS, which may represent a component itself of MS. Conversely, OSAS may well induce insulin resistance, high blood pressure, hyperglycemia and hyperlipidaemia which may predispose to MS and ultimately to type 2 diabetes mellitus. Co-occurrence of these two conditions increases remarkably the risk for cardiovascular events and mortality.

Table 5
Some clinical and metabolic characteristics in diabetic and non-diabetic OSA patients.

	Diabetes	Non-diabetes	p
	n = 46	n = 177	
Age	58.6 ± 8.3	53.6 ± 11.6	0.008
Body mass index (kg/m^2)	34.3 ± 4.5	32.1 ± 6.0	0.009
Waist circumference (cm)	116.9 ± 11.1	110.0 ± 13.5	0.001
SCORE metabolic syndrome	3.78 ± 0.84	2.49 ± 1.22	0.000
Hypertension*	91.3%	67.8%	0.001
Central obesity*	93.5%	80.9%	0.028
Hypertriglyceridemia*	56.5%	37.9%	0.018
Low HDL-cholesterol*	47.8%	37.4%	0.131
Metabolic syndrome*	97.8%	54.0%	0.000

*According to ATP III criteria.

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5. Learning points

- This is a large study assessing the association between OSAS and the metabolic syndrome in an internal medicine clinical setting.
- The main finding is the high prevalence of OSAS in male and female heavy snorers with the clinical features of the metabolic syndrome.
- Although causality between OSAS and metabolic syndrome has not been demonstrated yet, and a bidirectional association between the two may be postulated, the co-occurrence of the two conditions may remarkably increase the risk for cardiovascular events.

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