



Metabolic syndrome in non-obese patients with OSA: learning points of a cross-sectional study from a tertiary care hospital in Central India

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Abstract

Study objectives Obesity is often considered mandatory for the diagnosis of Metabolic Syndrome (MS). Data on the prevalence of MS in non-obese patients with Obstructive Sleep Apnea (OSA) is scarce. This study was aimed to determine the prevalence of MS in non-obese patients with OSA.

Methodology All consecutively diagnosed patients with OSA between October 2018 and November 2019 were screened for metabolic syndrome. Patients with OSA and BMI < 25 kg/m² (NOOSA) vs BMI > 25 kg/m² (obese OSA) were compared. Lean waist NOOSA was defined as BMI < 25 kg/m² and WC < 80 cm (32 in.) for women or < 90 cm (36 in.) for men.

Results During the study period, 502 patients were diagnosed with OSA. MS was observed in 35% of patients with NOOSA compared to obese patients with OSA (79%). In the NOOSA group, hypertension, impaired fasting glucose, diabetes mellitus and dyslipidemia were observed in 65, 48, 14 and 61% respectively and all of these parameters were significantly more common in the obese group ($p < 0.001$). Parameters of OSA severity (apnea-hypopnea index or AHI, time spent below 90% saturated or T90, and nadir oxygen) were significantly more severe in the obese group with OSA. Approximately 83% of patients in the NOOSA group had at least two metabolic risk factors, compared to the obese OSA group, in which 95% had two or more metabolic risk factors. Sixty-four percent of patients with NOOSA with lean waist had at least two metabolic risk factors. At BMI cut-offs of < 25, < 27 and < 30 kg/m²; 35, 46 and 57% of patients with OSA respectively had metabolic syndrome.

Conclusion Metabolic syndrome was observed in approximately one in three patients with OSA and BMI < 25 kg/m². Approximately two of every three lean waist non-obese patients with OSA had at least two markers of metabolic syndrome. The role of OSA in the development of metabolic syndrome in non-obese individuals needs further exploration.

Keywords Obstructive Sleep Apnea · Metabolic syndrome · Nonobese · Continuous positive airway pressure

Introduction

Obstructive Sleep Apnea (OSA) is a highly prevalent disorder that leads to significant cardiovascular complications, insulin resistance, hypertension (HTN) and dyslipidaemia [8]. OSA has striking similarities with metabolic syndrome (MS), which is a cluster of metabolic risk factors [22]. The high prevalence of

MS in patients with OSA (43–78%) shows the close association between these two disorders [1, 6, 41, 44]. The presence of both of these disorders in the same patient is also known as Syndrome Z.

With changing lifestyles and eating habits, obesity and associated diseases have taken the shape of a pandemic. OSA and MS are both known to be associated with obesity. Asians are known to develop abdominal obesity or apple-shaped obesity, where the abdominal girth is more than the hip circumference [33]. Despite lower weight and BMI, Asians are at greater risk of developing cardiovascular complications than Caucasians matched for BMI [33]. Therefore, the cut-off for obesity (BMI) has been lowered from 30 kg/m² to 25 kg/m² in Asians. Similarly the waist circumference cut offs for defining MS has also been lowered for Asians [33].

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One of the most important features of MS is obesity. Therefore, in non-obese individuals, MS is often not suspected and is neglected. It has been shown that non-obese individuals may also be prone to developing MS. These patients have been labelled nonobese MS or MONO (Metabolically Obese Non Obese) [30]. There is scarce information on MS in lean Indians; the prevalence of MS in lean individuals (BMI < 25 kg/m²) was found to be 12.6 and 20.4% in two studies from India [12, 34]. In the Indian population, using a BMI < 25 kg/m² cut off was associated with increased sensitivity of OSA questionnaires [38]. Non-obese OSA is now a known entity; 25% of OSA cases were non-obese in a study from the USA [18]. Data on the prevalence of MS in non-obese OSA are scarce. In a few of the earlier studies from China and Japan, 19–39.6% of non-obese OSA had at least two components of MS [2, 25, 30].

The present study was aimed to determine the prevalence of MS in patients with non-obese OSA (NOOSA).

Methods

Study setting and participants

This cross-sectional study was done in consecutive patients with OSA diagnosed in our sleep laboratory (October 2018–November 2019). An article comparing the prevalence of syndrome Z in men and women has already been published from this Study [10]. All patients were evaluated for MS according to the NCEP-ATP III [22]. MS was defined as presence of three or more of following features:

1. Large waist circumference (Asian cut-off was used) [3]: Waist Circumference (WC) \geq 80 cm (32 in.) for women or \geq 90 cm (36 in.) for men.
2. High triglyceride level: \geq 150 mg/dL
3. Reduced high-density lipoprotein (HDL) cholesterol — < 40 mg/dL in men or < 50 mg/dL in women
4. Increased blood pressure — systolic blood pressure \geq 130 mmHg and/or diastolic blood pressure \geq 85 mmHg or current use of antihypertensive drugs
5. Elevated fasting blood sugar — \geq 100 mg/dL or patients already on oral hypoglycemics.

Metabolic scores were counted as the sum of number of the aforementioned factors found positive. Dyslipidemia was defined as either raised TG or Low HDL level (as mentioned in the foregoing definitions).

- Inclusion Criteria: a) All patients diagnosed with OSA by level I PSG.
b) Age \geq 18 years.

c) Patients willing to participate in the study.

Exclusion Criteria: a) People not giving consent to draw blood sample b) AHI < 5 on level I PSG c) Body Mass Index > 25 kg/m².

Procedures

All patients underwent level I PSG (Philips Respironics Alice 6). Apneas and Hypopneas were scored according to AASM scoring manual 2012 [7]. If a patient was diagnosed as having moderate or severe OSA (AHI > 15), then the patient was manually titrated in the sleep lab with PAP according to AASM protocol [27]. Each sleep study was manually scored and cross checked by a sleep consultant. The severity of OSA was determined by apnea-hypopnea index (AHI). OSA was defined as mild (5–14.9), moderate (15–29.9) or severe (\geq 30) on the basis of AHI. Nadir oxygen levels (minimum oxygen saturation during sleep) and percentage of total time with oxygen saturation level lower than 90% during sleep (T90) were also compared between non-obese and obese patients with OSA. Sleepiness was defined if the Epworth sleepiness score (ESS) was more than 10.

Blood investigations

All patients diagnosed with OSA underwent blood testing in the morning after overnight fasting for fasting blood sugar (FBS) and lipid profile (total cholesterol, triglyceride, low-density lipoprotein, very low-density lipoprotein and high density lipoprotein) by fully automated chemistry analyser (AU680, Beckman Coulter).

Anthropometry and general examination

Waist was defined at the point midway between iliac crest and lower costal margin and waist measurement was performed during normal breath out with tape snugly fitted and horizontal to floor while the subject stood. Hip circumference was measured around the widest portion of the hips with tape snugly fitted and horizontal to floor while the subject stood with arms at the sides, feet close together. Neck circumference was measured at the level of the cricothyroid membrane with tape while patient in standing position. Blood Pressure was measured after 10 min in the sitting position; first reading was discarded. Average of second and third reading of blood pressure was taken. Weight was measured by Seca® weighing machine and height was measured by SECA® stadiometer. BMI was calculated as {weight (kg)/height (m)²}. Non-obese OSA (NOOSA) was defined as patients having BMI < 25 kg/m² and obese was defined as patients with BMI \geq 25 kg/m². Lean waist NOOSA was defined as BMI < 25 kg/m² and WC < 80 cm (32 in.) for women or < 90 cm (36 in.) for men.

Ethics and permissions

Protocol of this study was reviewed and approved by Institutional Human Ethics Committee (IHEC) of AIIMS Bhopal (IHEC-LOP/2018/MD0014 dated 17 October 2018). A participant information sheet in the Hindi language was given to eligible participants and their queries if any were resolved. Written informed consent was obtained from those who were willing to participate.

Data analysis

Data analysis was done using R software [39], *ggplot2* [43] and *gtsummary* [42] packages. We have summarized nominal variables with count and percentage and numerical variables with mean and its standard deviation. We have stratified our data across those who had BMI ≥ 25 and BMI < 25 as well as those who were thin and obese (based on waist circumference). Then we tested differences in distribution of numerical and categorical variables across these groups by using t-test and Chi-square test respectively. A *p*-value less than 0.05 was considered to be statistically significant. The prevalence of MS was estimated as *q* percentage and its 95% confidence interval was calculated.

Results

During the study period, 502 patients (357 men; 145 women) were diagnosed with OSA (AHI > 5) [10]. Mean BMI was 31.6 ± 11.1 kg/m² (women: 35.3 ± 7.2

and men: 30.1 ± 12.0 kg/m²) ($p < 0.001$). Of 502 patients with OSA, 69 (14%) had BMI < 25 kg/m² (NOOSA). Of these 69 patients in the NOOSA group, 24 met the definition of metabolic syndrome and thus the prevalence of metabolic syndrome in OSA patients with BMI < 25 kg/m² was 35% (95% CI 25 to 47) (Fig. 1). Various clinical parameters across OSA patients with BMI < 25 kg/m² and BMI > 25 kg/m² (obese OSA) were compared (Table 1). MS was seen in 35% of patients with NOOSA compared to 79% in obese patients with OSA. Metabolic scores were higher in the obese group (3.4 ± 1.1) compared to 2.2 ± 1.0 in the NOOSA group ($p < 0.001$).

In the NOOSA group, hypertension, impaired fasting glucose, diabetes mellitus and dyslipidemia was seen in 65, 48, 14 and 61% respectively and all these parameters were significantly more common in the obese group. Parameters of OSA severity (AHI, T90 and nadir oxygen) were significantly more severe in the obese OSA group. Sleepiness (Epworth sleepiness scale (ESS) > 10) was more commonly seen in the obese group (41 vs 23%) and mean ESS was also higher in the obese group.

Of patients with NOOSA with lean waist, 64% had at least two metabolic risk factors (Table 2). In the lean waist NOOSA group, HTN, impaired fasting glucose, diabetes mellitus and dyslipidemia was seen in 64, 51, 15 and 61% respectively and all these parameters were significantly more common in the obese group.

At different cut-off values of BMI (< 25 , < 27 and < 30 kg/m²) were used: 34.8, 45.5 and 57.4% had MS respectively. (Table 3).

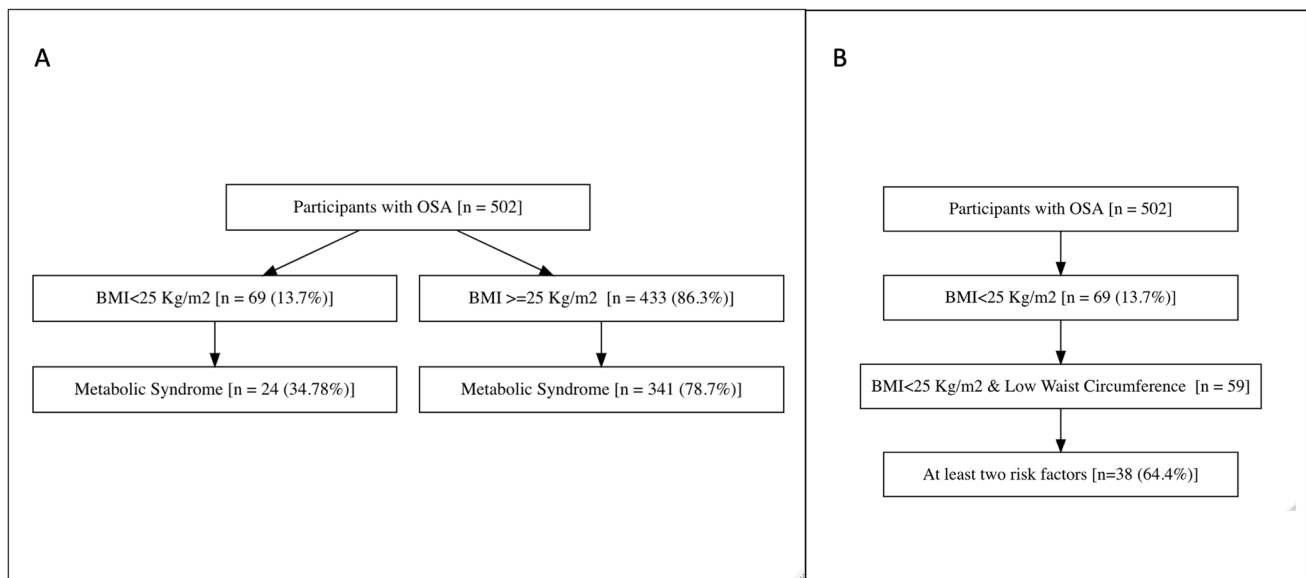


Fig. 1 **A** Metabolic syndrome prevalence in patients with OSA (< 25 kg/m²—Non-Obese OSA) and those with BMI ≥ 25 kg/m². **B** Showing presence of at least two metabolic factors in patients with lean waist non-obese patients with OSA (BMI < 25 kg/m² and lean waist)

Table 1 Comparison of non-obese OSA patients (BMI < 25 kg/m²) with obese OSA (BMI > 25 kg/m²) patients

Characteristic	Overall, N = 502	BMI in kg/m ²		p-value
		< 25, N = 69 (14%)	25+, N = 433 (86%)	
Age	51.9 (12.2)	49.5 (15.4)	52.2 (11.6)	0.162
Gender				0.001
Female	145 (29%)	8 (12%)	137 (32%)	
Male	357 (71%)	61 (88%)	296 (68%)	
Metabolic Syndrome				< 0.001
No MS	137 (27%)	45 (65%)	92 (21%)	
MS	365 (73%)	24 (35%)	341 (79%)	
Metabolic scores	3.2 (1.1)	2.2 (1.0)	3.4 (1.1)	< 0.001
Blood Pressure (mean (SD))				
Systolic Blood Pressure	133.4 (19.4)	131.6 (21.5)	133.7 (19.0)	0.437
Diastolic Blood Pressure	83.6 (12.3)	84.2 (13.5)	83.5 (12.1)	0.662
Fasting Blood Sugar (mean (SD))	110.4 (33.0)	100.7 (24.9)	111.9 (33.9)	0.001
Impaired fasting glucose	306 (61%)	33 (48%)	273 (63%)	0.023
Triglyceride (mean (SD))	148.2 (70.0)	146.5 (74.4)	148.5 (69.3)	0.834
Raised Triglyceride	176 (35%)	20 (29%)	156 (36%)	0.316
HDL (mean (SD))	41.6 (10.4)	41.8 (10.6)	41.6 (10.4)	0.864
Low HDL	281 (56%)	31 (45%)	250 (58%)	0.063
Heart disease	71 (14%)	9 (13%)	62 (14%)	0.918
Hypertension	395 (79%)	45 (65%)	350 (81%)	0.005
Diabetes Mellitus	145 (29%)	10 (14%)	135 (31%)	0.007
High Waist circumference	373 (74%)	10 (14%)	363 (84%)	< 0.001
Dyslipidemia	354 (71%)	42 (61%)	312 (72%)	0.080
AHI	62.8 (35.2)	35.9 (22.2)	67.0 (35.1)	< 0.001
Lowest oxygen (mean (SD))	77.0 (16.3)	83.2 (14.0)	76.0 (16.5)	< 0.001
T90 (mean (SD))	13.4 (24.1)	6.3 (18.2)	14.6 (24.8)	0.001
ESS Total (mean (SD))	8.2 (5.0)	6.3 (4.2)	8.5 (5.1)	< 0.001
ESS < 10	308 (61%)	53 (77%)	255 (59%)	0.007
ESS 10+	194 (39%)	16 (23%)	178 (41%)	

AHI, apnea hypopnea index; ESS, Epworth sleepiness scale; HDL, high density lipoprotein; OSA, obstructive sleep apnea; T90, percent sleep time spent with sPO₂ ≤ 90

Discussion

In this prospective cross-sectional study, MS was seen in approximately one in every three patients with OSA and BMI < 25 kg/m². Also, approximately two of every three (64%) patients with lean waist non-obese OSA had at least two markers of MS. Nonobese Indians with OSA are at much higher risk than other ethnicities for complications. OSA may be a neglected reason for development of MS in non-obese Indians. Our study highlights the necessity of evaluating MS, even in non-obese patients with OSA, so that early intervention can be implemented in these patients to prevent cardiovascular complications.

Over the last few decades, an increased prevalence of obesity has been reflected in a simultaneous increase in the prevalence of OSA. A four-year follow-up study of the Wisconsin sleep cohort reported that a 10% increase in weight was associated with a 32% increase in AHI and

a 10% weight reduction was associated with a 26% decrease in AHI [36]. There are multiple definitions of MS by different societies using various cut-offs for systolic and diastolic blood pressures, HDL, triglyceride and fasting blood sugar. But the presence of abdominal obesity is central to all definitions [23]. Both OSA and MS are known to be commonly present in obese individuals and often OSA and MS are overlooked in non-obese individuals. Data from the Wisconsin sleep cohort showed almost 14% and 5% of nonobese men and women (aged 50–70 years) respectively had moderate to severe OSA [37]. The community based HypnoLaus study from Switzerland (mean BMI of 25.6 kg/m²) showed very high rates of moderate to severe OSA (approximately 23% in women and 50% in men) [20]. In our current study done at a referral sleep centre, 14% of the OSA population had BMI < 25 kg/m². Non-obese men with OSA have been shown to have higher levels of visceral fat compared to subjects without OSA [26]. Metabolic parameters including

Table 2 Comparison of lean waist NOOSA patients (BMI < 25 kg/m² and lean waist[#]) with other subjects (include obese as well as non-obese but non lean waist)

Characteristic	Lean Waist NOOSA N = 59 (12%)	Others N = 443 (88%)	p-value
Age	47.9 (15.6)	52.4 (11.6)	0.038
Gender			
Women	6 (10%)	139 (31%)	0.001
Men	53 (90%)	304 (69%)	
Blood Pressure {mean (SD)}			
Systolic Blood Pressure	131.1 (22.7)	133.7 (18.9)	0.396
Diastolic Blood Pressure	84.4 (14.4)	83.5 (12.0)	0.647
Fasting Blood sugar {mean (SD)}	100.8 (26.2)	111.7 (33.6)	0.005
Impaired Fasting Glucose	30 (51%)	276 (62%)	0.121
Triglyceride {mean (SD)}	149.8 (79.6)	148.0 (68.7)	0.870
High Triglyceride	19 (32%)	157 (35%)	0.731
High density Lipoprotein (HDL) {mean (SD)}	42.1 (10.9)	41.5 (10.4)	0.696
Low HDL	26 (44%)	255 (58%)	0.068
Heart disease	8 (14%)	63 (14%)	N.S
Hypertension	38 (64%)	357 (81%)	0.007
Diabetes mellitus	9 (15%)	136 (31%)	0.021
Dyslipidemia	36 (61%)	315 (71%)	0.151
Two of three parameters present*	38 (64%)	349 (79%)	0.021

[#]Waist circumference < 80 cm in females and < 90 cm in males

* Hypertension or Impaired Fasting Glucose or Dyslipidemia

NOOSA, non-obese obstructive sleep apnea; OSA, obstructive sleep apnea

Table 3 Proportion of MS in OSA patients at different cut off of obesity

BMI Cut-off (kg/m ²)	No MS		MS		p-value
	n	%	n	%	
< 25	45	65.2%	24	34.8%	< 0.001
25 +	92	21.2%	341	78.8%	
< 27	78	54.5%	65	45.5%	< 0.001
27 +	59	16.4%	300	83.6%	
< 30	103	42.6%	139	57.4%	< 0.001
30 +	34	13.1%	226	86.9%	

BMI, body mass index; MS, metabolic syndrome; OSA, obstructive sleep apnea

triglycerides, cholesterol and inflammatory markers are elevated in non-obese men with OSA compared to controls [26].

Expectedly NOOSA had less severe OSA (in terms of AHI, T90 and nadir oxygen) compared to obese patients with OSA. NOOSA also had less severe metabolic factors than obese patients with OSA. But the prevalence of markers of MS was significantly higher than seen in non-obese individuals from the general population.

MS in non-obese general population

In an Indian study done in general population, 1710 out of 2350 people had BMI < 25 kg/m² and 355/1710 (20.4%) had

MS [12]. These were called Metabolically Obese No Obese (MONO). In a multi-ethnic study done in Malaysia, prevalence of MONO was 11.7% and it was highest in people from Indian origin (39.3%). The prevalence of MONO is reported from 4.6–12.7% from big community based studies from the USA, Korea, and Iran [19, 28, 32, 35] Compared to 4.6–20.4% in the community population; 35% of nonobese patients with OSA in our current study had MS.

OSA and MS have a bidirectional relationship and they fuel each other. MS is linked to increased cardiovascular complications. OSA may promote the onset of MS through several mechanisms: increased sympathetic activity, intermittent hypoxemia, hypothalamic–pituitary–adrenal axis dysfunction, impaired endothelial function, and abnormal

production of inflammatory cytokines and adipokines. In a study of follow-up of two population-based cohorts (from Brazil and Switzerland) association between the presence of OSA and the incidence of MS was assessed [21]. Approximately 17% participants without baseline MS developed MS after follow up of 6 years. In this study, moderate-to-severe OSA was independently associated with the development of MS (OR 2.58, 95% CI 1.61–4.11).

MS in non-obese OSA

Asians are at higher risk of developing cardiovascular complications at a lower BMI and at a younger age compared to Caucasians. So the cut off for both WC to define MS and BMI were lowered, since these lower cut off could better predict patients at risk. Even when a BMI cut off of 25 kg/m² was used, patients with OSA had a significantly higher proportion of HTN, IFG, DM, dyslipidemia and MS in our study. Approximately half of nonobese patients with OSA in the current study had impaired fasting glucose and two thirds had hypertension, which is significantly higher than that seen in general Indian population [4, 5].

We could find only three studies in the English literature, in which components of MS were assessed in nonobese patients with OSA. Two studies from Japan used Japanese Diagnostic Standards for MS and excluded patients with WC > 85 cm [2, 25]. Similarly, a Chinese study used NCEP ATP III criteria, but excluded patients with WC > 80 and 90 in women and men respectively [30]. All these studies assessed the presence of at-least two of three metabolic parameters (hypertension, impaired fasting glucose and dyslipidemia): 19–39.6% of non-obese OSA had at least two of three components [2, 25, 30]. We used similar criteria as the Chinese study and found 64% of lean waist non-obese patients had two of three metabolic parameters present, which was significantly higher than found in previous studies (Table 4).

South Asians living in the UK were found to have a higher prevalence and more severe OSA than BMI-matched Europeans [29]. As Asians are probably at higher risk of severe OSA; higher prevalence of parameters of MS in lean waist

NOOSA seen in our study also hints that probably non-obese Asians with OSA are at greater risk to develop MS compared to other ethnicities and this aspect needs further exploration.

Continuous positive airway pressure (CPAP) has been shown to have some beneficial effects on individual metabolic components of MS [11]. Treatment of OSA has been shown to improve symptoms of sleep apnea, particularly excessive daytime sleepiness, and lowers blood pressure. CPAP can reduce cardiovascular disease risk and may improve diabetes control [31]. Non-obese patients with OSA were found to have lower CPAP adherence than obese patients with OSA possibly due to a low respiratory arousal threshold [18]. Comprehensive management including weight reduction, active life style, dietary weight loss, and regular CPAP usage are keys for management of this syndrome Z (OSA and MS).

OSA has been associated with cardiovascular, neurological complications and poor quality of life [9, 15–17]. MS, DM, HTN, fatty liver disease, OSA and Coronary artery disease are inter-connected in many ways. With changing lifestyle and dietary habits, obesity and associated diseases are increasing significantly. Both MS and OSA have been associated with increased risk of COVID-19 related infection and complications [24, 40]. We believe that even in non-obese patients with OSA, MS should be screened and if present they should be aggressively managed with both life style modification and CPAP.

OSA is much neglected disease worldwide and this is even more true for non-obese individuals, where OSA is often not even considered in the differential diagnosis [13, 14].

Strengths and limitations

Our study had several strengths. (i) To the best of our knowledge, it is first Indian study on the prevalence of MS in non-obese OSA (ii) A level I PSG was done in all subjects (iii) The most widely accepted criteria for MS i.e. NCEP-ATP III were used for diagnosis. Limitations of the study were that there were fewer participants in the NOOSA group and therefore the prevalence estimates have a wide confidence

Table 4 Summary results of studies on metabolic syndrome among non-obese OSA

Author	Country	Sample size	Prevalence	Criteria
Kono M. et al	Japan	42	8 (19%)	BMI < 30 kg/m ² and Visceral Fat A was 90 cm
Akahoshi et al	Japan	101	40 (39.6%)	Subjects who had BMI ≥ 25 and waist circumference at ≥ 85 were excluded
Qi-Chang Lin et al	China	113	44 (38.9%)	Subjects who had BMI ≥ 25 and waist circumference at ≥ 90 cm in men and ≥ 80 cm in women were excluded
Present study	India	59	38 (64%)	

Subjects with at least two of the following: hypertension, hyperglycemia and dyslipidemia
BMI, Body Mass Index

interval. Also, being a cross-sectional study, temporality of the presence of MS and OSA or vice-versa could not be established. Participants were selected from patients with OSA in a referral sleep clinic; this selection process may have resulted in an overestimation of the prevalence of MS in this study.

Conclusions

To conclude, metabolic syndrome is highly prevalent in the non-obese population with OSA (35%); 64% of lean waist non obese OSA patients had at-least two markers of metabolic syndrome. All patients with OSA, even if nonobese should be screened for MS so that early intervention can be implemented in these patients to prevent cardiovascular complications.

Abbreviations AHI: Apnea hypopnea index; BMI: Body mass index; CPAP: Continuous positive airway pressure; MS: Metabolic syndrome; NCEP-ATPIII: National cholesterol education program adult treatment panel III; NOOSA: Non-obese OSA; OSA: Obstructive sleep apnea

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Author contribution PC: Data collection, analysis.

AG: Conceptualized, data collection, analysis and manuscript writing.

AP: Data collection, analysis.

SG: Conceptualized and manuscript writing.

AK: Conceptualized and manuscript writing.

MAR: Data collection.

VA: Data collection.

Declarations

Ethics approval and consent to participate This is a retrospective analysis study and waiver of this study was taken from ethical clearance committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interests.

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