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Original Article

Prevalence and risk factors of syndrome Z in urban Indians ☆

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ABSTRACT

Background: Syndrome Z is defined as the co-occurrence of obstructive sleep apnea (OSA) and metabolic syndrome. There is a paucity of information on the magnitude of syndrome Z in the community and the factors associated with it.
Methods: We conducted a two-stage, cross-sectional, community-based study in four different socioeconomic zones of the South Delhi district, India, from April 2005 through June 2007. In stage 1, a systematic random sample of subjects of either gender aged 30–65 years were administered a questionnaire by door-to-door survey. Subjects that responded were classified as habitual and non-habitual snorers. In stage 2, all the habitual and 10% of randomly selected non-habitual snorers were invited for overnight polysomnography and evaluation for metabolic syndrome. The National Cholesterol Education Program–Adult Treatment Panel III (NCEP–ATPIII) criteria were used to define metabolic syndrome.
Results: Of the 2860 subjects approached, 2505 (88%) completed stage 1; 452 (18%) were habitual snorers. In stage 2, OSA (defined as apnea–hypopnea index $\geqslant 5$) was observed in 94 (32.4%) of 290 habitual snorers and 3 (4%) of 75 non-habitual snorers. Seventy (77%) of the 91 habitual snorers with OSA also had metabolic syndrome; none of the non-habitual snorers with OSA had metabolic syndrome. The estimated population prevalence of metabolic syndrome was 43% [95% CI: (41.0–44.9%)] and syndrome Z was 4.5% (95% CI: 3.7–5.3). On multivariable analysis, age [OR: 1.05 (1.00–1.09)], male gender [OR: 5.64 (2.06–15.49)], percent body fat [OR: 1.08 (1.04–1.13)] and ΔSaO_2 (%) (defined as the difference between baseline and minimum SaO_2 during overnight sleep study) [OR: 5.80 (2.36–14.26), 17.70 (5.97–52.17) and 57.1 (19.12–170.40) for 10–20%, 20–30% and >30% reduction respectively as compared to <10% reduction] were independently associated with syndrome Z.
Conclusions: To the best of our knowledge, this is the first population-based study on the prevalence and risk factors of syndrome Z, and it reveals that a considerable proportion of community-dwelling northern Indian adults have syndrome Z. Age, male gender, percent body fat and severity of nocturnal desaturation were independent risk factors for syndrome Z.

1. Introduction

Obstructive sleep apnea (OSA) is associated with increased cardiovascular and cerebrovascular morbidity and mortality [1–4]. Its interaction with various vascular risk factors (metabolic syndrome) has long been recognized [5]. Metabolic syndrome, the clustering of metabolic and morphological risk factors including insulin resistance, is a well established risk factor for cardiovascular disease [6]. Investigations have shown that OSA is independently associated with various vascular risk factors such as hypertension [7,8], insulin resistance [9,10] and dyslipidemia [11,12].

It has been recently shown that OSA is associated with metabolic syndrome, independent of obesity [11]. The relative role of

Abbreviation: AHI, apnea–hypopnea index; OSA, obstructive sleep apnea; PSG, polysomnography; BMI, body-mass index.

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obesity and OSA in the pathogenesis of metabolic syndrome is far from clear [13]. Both OSA and metabolic syndrome are highly prevalent in middle-aged adults. Population-based studies from Asia have shown that OSA occurs in 9–24% of middle-aged adults [14,15]. Prevalence of metabolic syndrome among Asians varies between 21% and 41% based on the population studied and the definition used [16–18]. But the combined burden of OSA and metabolic syndrome (syndrome Z) has not been assessed at the population level so far. Estimation of this assumes importance given the multiplicative effect of OSA and metabolic syndrome on cardiovascular disease. A small hospital-based pilot study from Singapore showed a very high prevalence of syndrome Z (nearly 95%) in patients with metabolic syndrome [19]. Given the association of OSA with cardiovascular disease, it is prudent to hypothesize that OSA may promote metabolic syndrome. Nevertheless, data on the association between OSA and metabolic syndrome are conflicting [20–23]. Further, some of the studies also suggest obesity to be an important confounder as it is also associated with several comorbid conditions including OSA, type 2 diabetes mellitus, hypertension and cardiovascular diseases [23,24].

The present study was aimed to estimate the prevalence of syndrome Z in a northern Indian community using data from the South Delhi sleep study which estimated the population prevalence of OSA. The factors associated with syndrome Z were also studied.

2. Methods

2.1. Study population: South Delhi sleep study

The South Delhi sleep study was a two-stage cross-sectional study aimed at determining the prevalence and risk factors for OSA in middle-aged urban Indians. The study design, inclusion and exclusion criteria, recruitment methods, and evaluation of study subjects are detailed elsewhere [25]. The study was approved by the institutional ethics committee and written informed consent was taken from all subjects. All subjects approached were administered a questionnaire to assess their snoring habit in the first stage. In stage 2, all the habitual snorers and 10% of randomly selected non-habitual snorers were invited for overnight polysomnography and evaluation for metabolic syndrome. Habitual smoking/drinking was defined as smoking/alcohol intake for at least three times a week. The PSG studies were scored manually according to standard criteria by trained technicians [26,27]. OSA was defined as apnea–hypopnea index (AHI) $\geqslant$ 5. Patients were characterized as having mild (AHI 5–15 events/h), moderate (15–30) and severe OSA (>30 events/h) based on their AHI score. ΔSaO_2 (%) was calculated as the difference between baseline SaO_2 and minimum SaO_2 during sleep.

2.2. Anthropometry

A detailed physical examination was performed in which height, weight, body-mass index (BMI, kg/m^2), neck length, neck circumference, waist and hip circumference were measured and the waist–hip ratio was calculated. Body weight was recorded (to the nearest 0.5 kg) in erect posture without footwear and wearing only light indoor clothes. Percent body fat was estimated by bipedal bio-electric impedance using a body composition analyzer (Tanita body composition analyzer – TBF 300 GS, Tokyo). Waist circumference was measured midway between the lower rib margin and the anterior superior iliac spine. Skin fold thickness was measured using Lange skin fold calipers (Beta Technology Inc., Santa Cruz, CA) to the nearest mm. The mean value of three readings was recorded for each measurement.

2.3. Blood pressure recording

Blood pressure was measured with a mercury sphygmomanometer to the nearest 2 mm Hg, in sitting position, after at least 5 min of rest. It was recorded as the mean of three measurements taken at 1 min intervals. A history of antihypertensive medication intake was also recorded in hypertensive subjects.

2.4. Biochemical tests

At the end of the sleep study, blood samples were taken to estimate fasting blood glucose (glucose oxidase method) and lipid profile (total cholesterol, LDL, VLDL, HDL, triglycerides). Total cholesterol, triglycerides and HDL–cholesterol were measured using immunocolorimetric assay while LDL–cholesterol was derived indirectly using the Freidwald equation.

2.5. Metabolic syndrome

Metabolic syndrome was defined using the National Cholesterol Education Program–Adult Treatment Panel III (NCEP–ATPIII, 2001) criteria [28]. But the cut-offs for defining abdominal obesity based on waist circumference were taken as $\geqslant$90 cm in men and $\geqslant$80 cm in women, as recommended by the World Health Organization guidelines for South Asians [29].

2.6. Syndrome Z

Syndrome Z was defined as co-occurrence of OSA with metabolic syndrome [5].

2.7. Statistical analysis

Continuous variables were summarized as mean ± SD or median (IQR) and categorical variables as proportions (%). Comparison of quantitative characteristics between subjects with and without syndrome Z was done with the Student's *t*-test and qualitative characteristics compared using Chi-square test. Prevalence of metabolic syndrome and syndrome Z was calculated along with 95% CI. Logistic regression analysis was used to estimate the odds ratios of syndrome Z associated with different characteristics. A multivariable logistic regression was carried out to identify independent factors associated with syndrome Z. *P* values of <0.05 were considered significant. All analyses were performed on Stata 9.2.

3. Results

Fig. 1 depicts the study design and recruitment of subjects. Of the 365 subjects who underwent overnight PSG, 360 PSG studies were valid. Five studies were rejected due to insufficient sleep time (total sleep time <4 h); in addition, nine patients were excluded due to incomplete data on metabolic parameters. Finally, 351 patients were included in the analysis. Using AHI cut-off as 5 events/h, 94 of 351 subjects had OSA. The prevalence of OSA using weighted population was estimated as 9.3% (95% CI: 8.2–10.5%) [25].

3.1. Prevalence of metabolic syndrome and associated factors

Using the NCEP–ATPIII criteria, the prevalence of metabolic syndrome was found to be 43% (95% CI: 41.0–44.9%). The characteristics of subjects with and without metabolic syndrome (irrespective of OSA status) are shown in Table 1. Females had a higher risk of having metabolic syndrome as compared to males (OR = 1.57, 95% CI: 1.03–2.4). Subjects with metabolic syndrome were on the

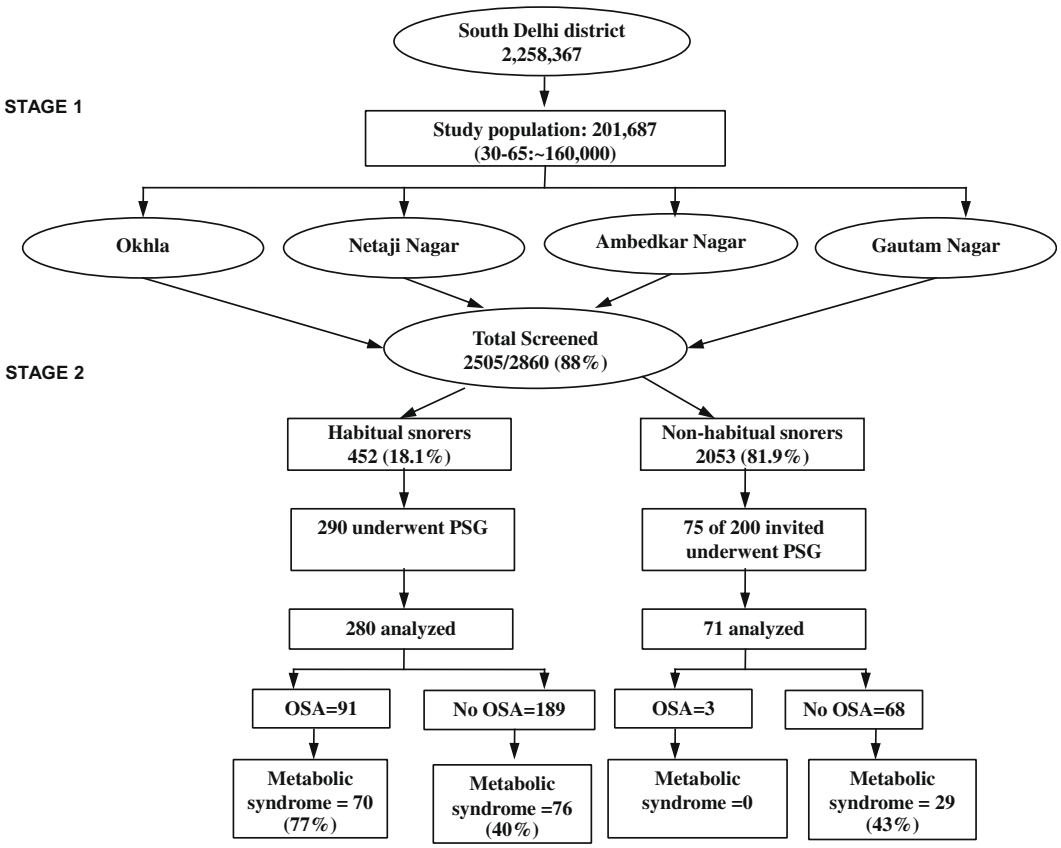

Fig. 1. Sampling strategy and the disposition of subjects through the study. PSG, overnight polysomnography; OSA, obstructive sleep apnea. *10 PSG studies in habitual snorers and four in non-habitual snorers were rejected in view of either insufficient total sleep time (<240 min) or incomplete data.

average 3.3 years older; had higher BMI; more percentage body fat, waist–hip ratio and waist circumference ($p < 0.001$). Subjects with metabolic syndrome had significantly more OSA events and also demonstrated a severe degree of nocturnal desaturation ($\Delta SaO_2 > 30\%$, $p < 0.001$) compared to subjects without metabolic syndrome.

Multivariable analysis identified age, AHI score and percent body fat as independent predictors of metabolic syndrome (Table 3).

3.2. Prevalence of syndrome Z

Of 351 subjects, 70 had syndrome Z, giving rise to a population prevalence of 4.5% (95% CI: 3.7–5.3). Table 2 shows the characteristics of cases with and without syndrome Z. Age, BMI, percent body fat and waist–hip ratio were significantly higher in patients with syndrome Z. In addition, patients with syndrome Z demonstrated significant nocturnal desaturation (ΔSaO_2: $p < 0.001$).

3.3. Risk factors associated with syndrome Z

Age, male gender, percent body fat and nocturnal desaturation (i.e., ΔSaO_2) were independent risk factors for syndrome Z. An increasing trend of risk of syndrome Z was observed with increasing nocturnal desaturation (Table 4).

3.4. Gender-based analysis

Gender-based analysis with respect to various factors (results not shown) showed that females had higher BMI ($p < 0.001$), percent body fat (<0.001), waist circumference ($p = 0.03$) and higher prevalence of metabolic syndrome ($p = 0.04$) yet lower prevalence of syndrome Z than males. Furthermore, in comparison to females, males were found to have higher number of smokers and alcoholics ($p < 0.001$).

4. Discussion

In the present study we observed that nearly 5% of the middle-aged urban Indian adults had co-existent OSA and metabolic syndrome. In this population-based study we observed a high prevalence (43%) of metabolic syndrome. In addition, gender-based analysis (albeit univariate analysis) revealed a higher prevalence of metabolic syndrome in females. Similar findings have been reported previously [16,17].

We observed a significantly higher prevalence of metabolic syndrome in OSA patients and a significant association of metabolic syndrome with AHI. These are in agreement with reports on several other population groups [11,22,30,31]. These studies have reported five to ninefold risk of metabolic syndrome in subjects with OSA.

While most of the clinical and experimental studies provide circumstantial evidence to implicate OSA in the development of metabolic syndrome, its causal relationship has not been proved yet. Empirical evidence does seem to suggest that obesity is one of the major risk factors for OSA, and both OSA and obesity are associated with medical disorders such as type 2 diabetes mellitus, cardiovascular disease and increased mortality. Therefore, it may be an important confounder as it is known that about 70% of patients with OSA are obese and 40–90% of obese patients have OSA [32–34]. In view of these, such associations need to be interpreted with caution as the data are cross-sectional in nature. To be a cause or a

Table 1
Comparison of subjects with and without metabolic syndrome.

Characteristic	Metabolic syndrome		*p*	OR (95% CI)
	Present (*N* = 175)	Absent (*N* = 176)		
Age (years)	45.7 ± 9.0	42.4 ± 9.3	<0.001	1.04 (1.02–1.07)
Gender				
Female	87 (50)	68 (39)		1.00
Male	88 (50)	108 (61)	0.04	0.64 (0.42–0.97)
Body-mass index (BMI), (kg/m^2)	29.6 ± 5.1	25.3 ± 6.2	<0.001	1.15 (1.11–1.21)
BMI (kg/m^2)				
BMI < 25	30 (17)	95 (54)		1.00
BMI > 25	145 (83)	81 (46)	<0.001	5.67 (3.46–9.27)
Percent body fat	36.2 ± 11.3	26.4 ± 11.6	<0.001	1.07 (1.05–1.10)
Waist–hip ratio (W–HR)[b]				
Normal	34 (19.4)	76 (43.2)		1.00
Abnormal	141 (80.6)	100 (56.8)	<0.001	3.15 (1.95–5.09)
Waist circumference[b]				
Normal	6 (3.4)	62 (35.2)		1.00
Abnormal	169 (96.6)	114 (64.8)	<0.001	15.31 (6.41–36.60)
Smoking status				
Non-smokers	127 (73)	119 (68)		1.00
Smokers	48 (27)	57 (32)	0.31	0.79 (0.49–1.24)
Alcoholism				
Non-alcoholic	146 (83)	142 (81)		1.00
Alcoholic	29 (17)	34 (19)	0.5	0.83 (0.48–1.43)
Habitual snoring				
Non-snorers	29 (17)	42 (24)		1.00
Snorers	146 (83)	134 (76)	0.09	1.58 (0.93–2.68)
Habitual choking				
Absence of choking	127 (73)	151 (86)		1.00
Presence of choking	48 (27)	25 (14)	0.002	2.28 (1.33–3.91)
Epworth sleepiness score	7.1 ± 5.0	5.4 ± 4.0	<0.001	1.08 (1.03–1.14)
Excessive daytime sleepiness				
Absent	124 (71)	152 (87)		1.00
Present	51 (29)	24 (13)	0.001	2.60 (1.51–4.47)
Obstructive sleep apnea (OSA)				
Absent	105 (60)	152 (87)		1.00
Present	70 (40)	24 (13)	<0.001	4.22 (2.49–7.15)
Apnea–hypopnea index (AHI) (events/h)	2.3 (0–16.1)[a]	0 (0–1.83)[a]	<0.001	1.04 (1.02–1.06)
Severity of OSA				
No OSA	105 (60)	152 (86)		1.00
Mild	25 (14)	8 (4)		4.52 (1.96–10.41)
Moderate	16 (9)	9 (5)		2.57 (1.09–6.04)
Severe	29 (16)	7 (4)	<0.001	5.99 (2.53–14.20)
Duration of saturation				
<90% (min) [Median (IQR)]	3(0–27.25)	0(0–3.00)	<0.001	1.01 (1.00–1.01)
ΔSaO_2 (%)[c]				
$\Delta SaO_2 < 10$	84 (48)	118 (67)		1.00
$\Delta SaO_2 \geqslant 10$ & < 20	45 (25)	40 (22)		1.58 (0.95–2.63)
$\Delta SaO_2 \geqslant 20$ & < 30	16 (9)	11 (6)		2.04 (0.90–4.63)
$\Delta SaO_2 \geqslant 30$	30 (17)	7 (4)	<0.001	6.02 (2.52–14.35)

[a] Data presented as median (IQR), all other data presented as mean ± SD or *n* (%).
[b] Defining cut-offs were different for men and women – for W–HR > 0.95 and >0.88, respectively; for abdominal circumference $\geqslant$90 cm and $\geqslant$80 cm respectively.
[c] ΔSaO_2 = baseline SaO_2-minimum SaO_2 during sleep study.

risk factor for metabolic syndrome, OSA should have occurred prior to metabolic syndrome. To disentangle these aspects one should study newly diagnosed metabolic syndrome cases or conduct well planned cohort studies.

Coughlin and co-workers [11] found an independent overall association of OSA with the metabolic syndrome in a hospital-based study of 61 male subjects with OSA and 43 male controls. They used an AHI cut-off of >15 events/h to define OSA and NCEP–ATPIII criteria to diagnose metabolic syndrome. Similarly, Gruber and co-workers [22] also found an independent association of OSA with metabolic syndrome in a hospital-based cohort consisting of 38 subjects with OSA and 41 controls. To diagnose metabolic syndrome they used the International Diabetes Federation definition, [35] which shares many features with the NCEP-ATPIII definition but defines the cut-offs for waist circumference according to ethnicity. Similarly, Lam et al. [30] and Sasanabe et al. [31] (using criteria modified for the Japanese population [36]) demonstrated independent association of OSA with metabolic syndrome in Chinese and Japanese ethnic groups respectively.

While there are several studies that have compared the relationships between OSA and individual components of metabolic syndrome, besides the present study, only a few studies have reported an overall association of OSA with metabolic syndrome entity. Further, most of the studies have reported association of OSA with insulin resistance, as the latter is thought to be a central component of metabolic syndrome [37]. Data on the association of OSA and individual components of the metabolic syndrome are conflicting [9–12,20–23]. These discrepancies may be attributed to differ-

Table 2
Comparison of subjects with and without syndrome Z.

Characteristic	Syndrome Z		*p*	OR (95% CI)
	Present (*N* = 70)	Absent (*N* = 281)		
Age (years)	46.8 ± 8.6	43.3 ± 9.3	<0.01	1.04 (1.01–1.07)
Gender				
Female	22 (32)	133 (48)		1.00
Male	48 (68)	148 (52)	0.02	1.96 (1.12–3.42)
Body-mass index (BMI), (kg/m^2)	31.7 ± 5.6	26.4 ± 5.7	<0.001	1.16 (1.10–1.22)
BMI (kg/m^2)				
BMI < 25	7 (10)	118 (42)		1.00
BMI > 25	63 (90)	163 (58)	<0.001	6.51 (2.88–14.73)
Percent body fat	36.6 ± 12.8	29.9 ± 12	<0.001	1.04 (1.02–1.07)
Waist–hip ratio (W–HR)[b]				
Normal	9 (12)	101 (36)		1.00
Abnormal	61 (87)	180 (64)	<0.001	3.80 (1.82–7.98)
Waist circumference[b]				
Normal	0	68 (24)		
Abnormal	70 (100)	213 (75)	<0.001	
Smoking status				
Non-smokers	44 (63)	202 (72)		1.00
Smokers	26 (37)	79 (28)	0.14	1.51 (0.87–2.62)
Alcoholism				
Non-alcoholic	54 (78)	234 (84)		1.00
Alcoholic	16 (22)	47 (16)	0.23	1.47 (0.78–2.80)
Habitual snoring				
Non-snorers	0 (0)	71 (26)		
Snorers	70 (100)	210 (74)	<0.001	
Habitual choking				
Absence of choking	49 (70)	229 (82)		1.00
Presence of choking	21 (30)	52 (18)	0.03	1.89 (1.04–3.41)
Epworth sleepiness score	9.4 ± 5.8	5.4 ± 3.9	<0.001	1.19 (1.12–1.25)
Excessive daytime sleepiness				
Absent	36 (52)	240 (86)		1.00
Present	34 (48)	41 (14)	<0.001	5.53 (3.11–9.81)
Obstructive sleep apnea (OSA)				
Absent	0 (0)	257 (92)		
Present	70 (100)	24 (8)	<0.001	
Apnea–hypopnea index (AHI) events/h	26 (10.5–53)[a]	0 (0–1.6)[a]	<0.001	1.12 (1.09–1.16)
Duration of saturation				
<90% (min) [Median (IQR)]	37.5 (7.5–112.75)	0(0–3.00)	<0.001	1.02(1.01–1.02)
ΔSaO_2 (%)[c]				
ΔSaO_2 < 10	8 (11)	194 (69)		1.00
$\Delta SaO_2 \geqslant 10$ & < 20	20 (28)	65 (23)		7.46 (3.14–17.75)
$\Delta SaO_2 \geqslant 20$ & < 30	13 (18)	14 (5)		22.51 (8.00–63.35)
$\Delta SaO_2 \geqslant 30$	29 (41)	8 (3)	<0.001	87.91 (30.61–252.41)

[a] Data presented as median (IQR), all other data presented as mean ± SD or *n* (%).
[b] Defining cut-offs were different for men and women – for W–HR > 0.95 and >0.88, respectively; for abdominal circumference $\geqslant$90 cm and $\geqslant$80 cm respectively;
[c] ΔSaO_2 = baseline SaO_2-minimum SaO_2 during sleep study.

ences in study populations (sleep clinic-based vs. community-based), ethnicity, or methodologies or inadequate power of the studies.

While age and percent body fat were common risk factors for both metabolic syndrome and syndrome Z, male gender and ΔSaO_2 were additional independent risk factors for syndrome Z. Gender-based analysis with respect to various factors (results not shown) showed that females had higher BMI, percent body fat, waist circumference, and higher prevalence of metabolic syndrome than males, yet females have lesser prevalence of syndrome Z. The lower prevalence of OSA in females and hence their protection towards syndrome Z could be attributed to lack of testosterone mediated aggravation of sleep disordered breathing and protective effect of female hormones [38]. Furthermore, smoking and alcoholism (as they are significantly higher in males [results not shown]) could also contribute to high prevalence of OSA and syndrome Z in males. To summarize, the present study indicates that 10 out of every 23 middle-aged urban Indians have metabolic syndrome and 1 out of every 10 with metabolic syndrome is a case of syndrome Z. This finding deserves special attention from India's public health perspective and could be attributed to the sedentary lifestyles adopted by most of the urban Indians in the background of a rapidly growing economy. Published literature with regard to syndrome Z is scanty and more research is required in this area. Such information is an indicator of risk prone nature of the population for various non-communicable diseases. Therefore, periodic assessment of these indicators in the various segment of the community would be helpful for public health management.

Table 3
Multivariable model with metabolic syndrome as an outcome variable.

Independent variable	Adjusted odds ratio (95% CI)	*p* value
Age	1.03 (1.00–1.05)	0.015
Apnea–hypopnea index	1.03 (1.02–1.05)	<0.001
Percent body fat	1.07 (1.05–1.09)	<0.001

Table 4
Multivariable model with syndrome Z as an outcome variable.

Independent variable	Adjusted odds ratio (95% CI)	*p* value
Age (for 1 year increase)	1.05 (1.00–1.09)	0.027
Gender		
Female	1.00	
Male	5.64 (2.06–15.49)	0.001
Percent body fat (for 1% increase)	1.08 (1.04–1.13)	<0.001
ΔSaO$_2$ (%)[*]		
ΔSaO$_2$ < 10	1.00	
ΔSaO$_2$ 10–20	5.79 (2.36–14.26)	<0.001
ΔSaO$_2$ 20–30	17.65 (5.97–52.17)	<0.001
ΔSaO$_2$ > 30	57.08 (19.12–170.37)	<0.001

[*] ΔSaO$_2$ (%) = baseline SaO$_2$-minimum SaO$_2$ during sleep study.

Strengths of the present study include (i) this is a systematically conducted population-based study that included subjects across all socioeconomic strata with a robust sample size (all other studies except one [Lam et al. [30]] being hospital-based); (ii) we diagnosed OSA in our patients on the basis of complete, in-hospital, supervised PSG studies, and we used an AHI cut-off of $\geqslant$5 events/h to diagnose OSA because the Sleep Heart Health Study suggested that OSA was associated with hypertension at respiratory disturbance index (RDI) thresholds as low as 5 events/h [7]; (iii) we defined the metabolic syndrome using the NCEP-ATPIII criteria which have been used extensively worldwide in epidemiological and clinical studies. A possible limitation of the present study may include self-selection bias, as more symptomatic subjects with a higher suspicion of OSA probably came forward for investigations on a voluntary basis.

To the best of our knowledge, this is the first population-based study that has investigated the prevalence and risk factors of syndrome Z. In conclusion, the prevalence of syndrome Z is considerable among middle-aged urban Indians. These findings emphasize the need for a high index of suspicion for the co-occurrence of OSA and metabolic syndrome in middle-aged urban Indians. Furthermore, preventive strategies, including lifestyle modifications, should be strongly advocated as a public health measure in the Indian population, which is overburdened with multiple cardiovascular risk factors.

5. Conflict of interest statement

None declared.

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Pfizer India Ltd. The sponsors had no role in study design, data analysis and in writing the manuscript.

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